THE HEBREW
UNIVERSITY
OF JERUSALEM

ELSC Annual Retreat 2021

Abstract Booklet

THE HEBREW UNIVERSITY OF JERUSALEM

Contents

THE HEBREW
UNIVERSITY
OF JERUSALEM

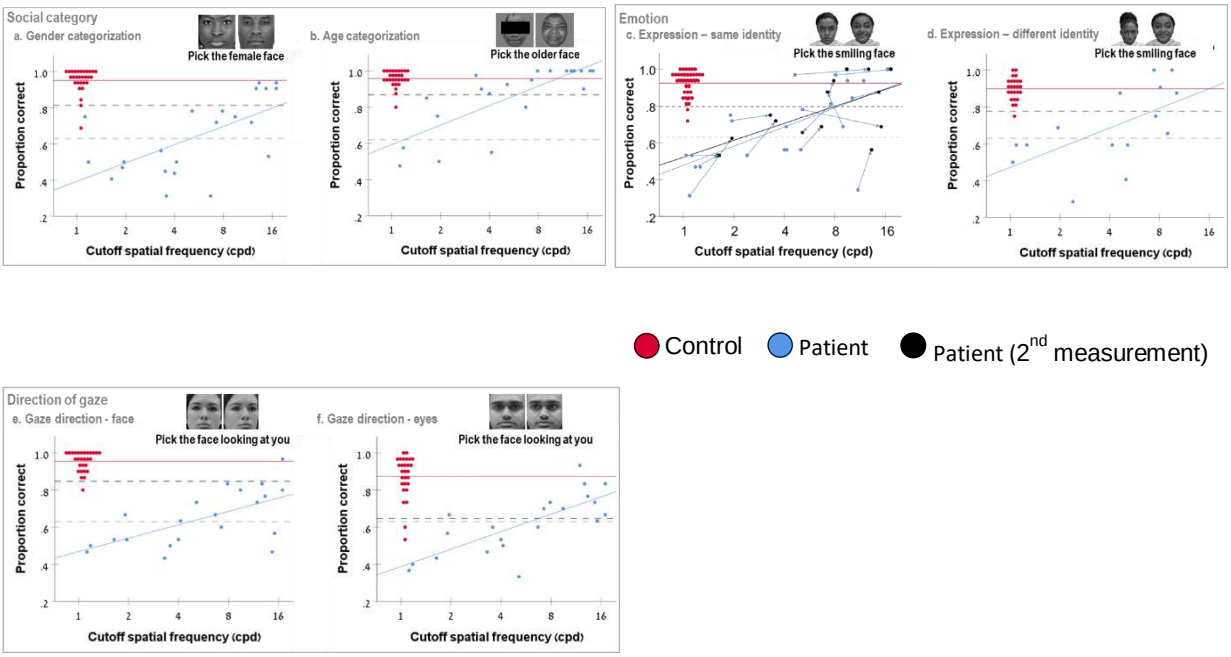
Sessions and Talks

THE HEBREW UNIVERSITY OF JERUSALEM

Social face understanding after prolonged early-onset visual deprivation

Asael Y. Sklar, Yuval Porat and Ehud Zohary

Humans can accurately tell the age, gender, current emotional state, and direction of gaze of person by a mere glimpse at his face. In normal development, this amazing capacity develops early, within the first year or two. Yet, what happens when early visual experience is lacking? We examined a unique population of Ethiopian children who had congenital bilateral cataracts that were surgically removed only in late childhood (Mean age at surgery 10.8 years). These children had extremely poor vision prior to cataract removal. After the operation, their visual acuity substantially improved, but the improvement varied considerably. As early as five months after cataract removal, many patients (but not all) were able to distinguish the social category of a face (i.e. age and gender), differentiate between emotional expressions and select a face with straight-ahead gaze based on head or eye orientation. Postoperative visual acuity was a major factor explaining the variance in the patients' performance across the face understanding tasks (see Figure). Crucially, control participants who did the same tasks under severe image blur, matching the conditions experienced by the patients with the *poorest* visual acuity, could perform the face understanding tasks extremely well. Thus, sufficient visual acuity is probably required for *learning* these tasks, but once acquired, useful facial information can be extracted even in conditions when the face is dramatically blurred. We conclude that there is no evidence for a critical period for the acquisition of social information from faces.



THE HEBREW
UNIVERSITY
OF JERUSALEM

Figure – Dispersion of the individual results in the face understanding tasks. Vertical axis denotes proportion of correct responses. Horizontal axis denotes participant's visual acuity at the time of the experiment, as measured by the cutoff frequency of their contrast sensitivity function (CSF). This cutoff frequency is the highest spatial frequency a given participant is able to perceive. All control participants saw blurred versions of the images such that they contained no spatial frequencies beyond 1.06 cycles per degree. Where needed, dots are dithered to prevent overlap. Horizontal lines indicate the level of performance significantly better than chance (P<0.05; lower hatched line); the mean of the control group (red line) and 2 SDs below this mean (upper hatched line), above which performance may be considered similar to that of typically developing controls

Advisor: Professor Ehud Zohary

THE HEBREW UNIVERSITY OF JERUSALEM

Uncovering the specificity of quantitative MRI to different molecular forms of iron in the brain

Shir Filo, Rona Shaharabani, Hanan Schoffman, Daniel Bar Hanin, Masha Adam, Naomi Habib, Tal Shahar, Aviv Mezer.

The main iron compounds, ferritin and transferrin, are distributed heterogeneously across the brain and are often implicated in neurodegenerative diseases. While quantitative MRI (qMRI) parameters such as R1 and R2* have been linked to brain tissue's microstructure, non-invasive discrimination between iron forms still remains a challenge. Here we present a new MR-relaxivity approach for increasing the sensitivity of MRI to different molecular forms of iron. First, we confirm in-vitro that different iron-bound proteins induce different relaxivities, which can be estimated with MRI. Remarkably, when examining the qMRI measurements of the R1-R2* interdependencies (R1-R2* slopes) we expose the intrinsic ferromagnetic properties of different iron forms. In the human brain we show that the in-vivo iron relaxivity, estimated by the R1-R2* slopes, provides a new MRI contrast. This contrast proves useful for enhancing the distinction between tumor tissue and non-pathological tissue. We further demonstrate that this new contrast allows to detect biological properties inaccessible by conventional MRI approaches. We confirmed this by comparing our in-vivo MRI contrast to RNA-sequencing and proteomics of resected tumor tissue. This unique in-vivo to ex-vivo strategy, along with group-level analysis on healthy subjects, are used to establish the sensitivity of the R1-R2* slopes to molecular iron forms in the brain. The R1-R2* slopes contrast allowed us to predict the inhomogeneous distribution of iron-binding proteins due to aging and across the brain, and to reveal differences in iron hemostasis between tumor tissues.

Advisor: Prof. Aviv Mezer

THE HEBREW
UNIVERSITY
OF JERUSALEM

Spatial learning in a complex environment

Ana Polterovich, Maciej M Jankowski, Alex Kazakov, Johannes Niediek, and Israel Nelken

We explore rat behavior and neuronal activity in a complex setting (the Rat Interactive Fantasy Facility, RIFF). The RIFF consists of a large circular arena (160 cm diameter) with 6 interaction areas (IAs) that each have a water port, a food port, and two loudspeakers. Rat behavior is monitored online using video tracking and nose-poke identification. Neural responses are recorded using telemetry (a 64-channel TBSI transmitter integrated in an Alpha-Omega SNR data acquisition system) or a logger on the head of the animal (RatLog-64, Deuteron Technologies).

We trained rats to perform a sound localization/discrimination task in the RIFF. Auditory cues consisted of 6 different modified human words that were played from each IA separately. When a rat reached the center of the arena, one of the sounds started playing once every 2 seconds, and the rat had to identify the correct location and collect a reward (food or water) within 20 seconds. Trials were otherwise terminated by access to a wrong port or by time out. Control tasks included pure localization and pure discrimination tasks. The rats were able to learn all the tasks rapidly without guidance. Neuronal responses to sounds were largely as previously described in anesthetized and passively-listening animals. However, neural activity in primary auditory cortex during behavior showed significant correlations with a range of non-auditory, behaviorally-related variables. These behaviorally-related responses were often expressed as slow, large changes in firing rates, and were stronger than auditory responses in primary auditory cortex.

Advisor: Prof. Israel Nelken

THE HEBREW
UNIVERSITY
OF JERUSALEM

Computation and learning in cortico-cerebellar loop models

Jonathan Kadmon

The cerebellum has a prominent role in learning and fine motor control. The immense granular layer—a distinctive anatomical feature of the cerebellar cortex—separates activity patterns and facilitates effective learning. While the theoretical foundations of stationary pattern separation by a sparse and expansive layer are well established, it is unclear how the cerebellum and cerebral cortex learn complex tasks in tandem.

Calcium imaging of motor cortex and cerebellar granule cells of mice trained on a simple motor task show that common representations in the two areas emerge concurrently during learning. These findings suggest a tight integration between the two brain regions. To understand the benefits of the joint dynamics, we consider a simple model composed of recurrent and feedforward networks, modeling the cortico-cerebellar loop. Based on ideas from reservoir computing, the model utilizes the distinct architecture of the cerebellum to circumvent the credit assignment problem. With theoretical arguments and simulations, I will show how the feedback and the expansive granular layer improve the fidelity of the circuit and reduce the overall task error. At the end of the talk, I will briefly present other open problems at the intersection of theoretical neuroscience and machine learning, on which we are working.

THE HEBREW
UNIVERSITY
OF JERUSALEM

The Gradient Clusteron: A Model Neuron that Learns to Solve Classification Tasks via Dendritic Nonlinearities, Structural Plasticity, and Gradient Descent

Toviah Moldwin

Synaptic clustering on neuronal dendrites has been hypothesized to play an important role in implementing pattern recognition. Neighboring synapses on a dendritic branch can interact in a synergistic, cooperative manner via nonlinear voltage-dependent mechanisms, such as NMDA receptors. Inspired by the NMDA receptor, the single-branch clusteron learning algorithm takes advantage of location-dependent multiplicative nonlinearities to solve classification tasks by randomly shuffling the locations of "under-performing" synapses on a model dendrite during learning ("structural plasticity"), eventually resulting in synapses with correlated activity being placed next to each other on the dendrite. We propose an alternative model, the gradient clusteron, or G-clusteron, which uses an analytically-derived gradient descent rule where synapses are "attracted to" or "repelled from" each other in an input- and location- dependent manner. We demonstrate the classification ability of this algorithm by testing it on the MNIST handwritten digit dataset and show that, when using a softmax activation function, the accuracy of the G-clusteron on the all-versus-all MNIST task (~85%) approaches that of logistic regression (~93%). In addition to the location update rule, we also derive a learning rule for the synaptic weights of the G-clusteron ("functional plasticity") and show that a G-clusteron that utilizes the weight update rule can achieve ~89% accuracy on the MNIST task. We also show that a G-clusteron with both the weight and location update rules can learn to solve the XOR problem from arbitrary initial conditions.

Advisor: Prof. Idan Segev

THE HEBREW
UNIVERSITY
OF JERUSALEM

Working memory training –what does it actually improve and how?

Amos David Boasson

Hundreds of studies tried to improve working memory with training, but they always compared “before” and “after” results. Our question is - what actually happens during training? Using behavioral methods and fMRI, we show that successful working memory training leads to the development of task-specific strategies, rather than enhancement in working memory capacity.

Advisor: Prof. Merav Ahissar

THE HEBREW UNIVERSITY OF JERUSALEM

Ventrolateral Striatum (VLS) Centric Neural Circuits Select Specific Orofacial Actions in Context-Dependent Manner

David Lipton

The Striatum is a brain region hub integrating sensorimotor drive with selective reinforcement to select appropriate action repertoires. Habits, compulsions, and addictions rely on plasticity within striatal circuits. The central question of my project is: **Within the broader ventrolateral striatum (VLS) orofacial and upper-limb striatal territory and relevant inter-connected basal ganglia subregions, how are individual actions relevant to these body parts encoded?** Is each orofacial action represented by a topographically defined subregion of the VLS? Or, at the other extreme, does the VLS as a whole broadly elevate the probability of a wide array of orofacial action, with the selection of the specific action chosen determined by other factors such as the contextual cues (i.e. stimuli) present in the animal's environment? I show here that both topographical location within the striatum and contextual information present in an animal's environment converge within the striatum to influence the distinct action produced by VLS direct-pathway neurons. Furthermore, activation of VLS indirect pathway neurons inhibits orofacial stereotypies, while leaving other types of behavioral expression unaffected. I then ask how the basal ganglia subregion directly downstream of VLS striatum, the SNR, conveys information from VLS-initiated neural activity to select individual orofacial actions. Here, preliminary data indicate that individual actions become more stereotyped and topographically encoded in the SNR, one step 'downstream' from striatum, and one step closer to motor output. Finally, I ask how cortical inputs to the VLS influence choice of action: I hypothesize that sensorimotor information pertaining to the current state/context the animal is in are represented in corticostriatal input to the striatum, and that these projections function to elevate striatal activity, preferentially in direct-pathway neurons, generating distinct behaviors that are appropriate to the given state/context. Surprisingly, despite stimulating corticostriatal inputs to the VLS under many different conditions, I have not been able to observe an effect of VLS-input stimulation on influencing behavior. I am currently continuing to investigate the role of these inputs in modulating neuronal activity in VLS-resident circuits and driving behavior.

Professor: Ami Citri

THE HEBREW
UNIVERSITY
OF JERUSALEM

Navigating by The Stars: The Role of Astrocytes in Spatial Cognition

Adi Doron

In recent years, groundbreaking research revealed many surprising roles for astrocytes in modulating neuronal activity and even behavior. While astrocytes in cortical areas were shown to respond to specific sensory stimuli, their activity in awake mice performing a multisensory cognitive task has not been studied. To investigate the functional role of astrocytes, we used 2-photon calcium imaging in dorsal CA1 of mice running in a virtual reality apparatus. We imaged dozens of astrocytes as mice ran in a familiar circular virtual maze, in which a reward was given in a constant location, and examined whether astrocytes independently encode spatial and non-spatial features of the environment. Astrocytes did not have bell-shaped tuning curves, typical to neuronal place cells, but rather appeared to increase their activity as they approached the previously learnt reward location. Using machine learning, we were able to successfully decode the mouse location from the astrocyte activity alone. We next imaged the same population of astrocytes while the mice were introduced to a novel virtual environment differing in visual and tactile cues. Notably, the astrocytic activity was no longer modulated by the location, suggesting that the elevation of activity towards a rewarding location requires familiarity with the environment. Our results shed light on the computational capabilities of astrocytes, their role in learning a new environment until it becomes familiar, and their contribution to cognitive functions.

Advisor: Prof. Inbal Goshen

THE HEBREW UNIVERSITY OF JERUSALEM

The processing of double negation

I-An Tan and Nir Segal

Overview This study aims to better understand the nature of negation processing cost. We know that sentences with overt (e.g., *no*, *not*) or covert (e.g., *less*, *few*) negative markers take more time to process than their affirmative counterparts (Wason 1959; Deschamps et al., 2015.) A common property for both kinds of markers is that they create a Downward Entailing (⇓) environment (you did*n't eat an apple*→you did*n't eat a green apple*), as opposed to negationless sentences which are Upward Entailing (⇑) (you *ate a green apple*→you *are an apple*). Two negative markers also induce an Upward Entailing environment (⇑).

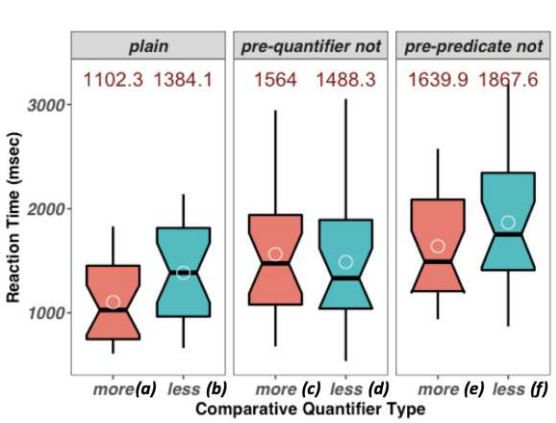
Is processing cost tied to negation, or to the entailment properties of sentences (Monotonicity)? We formulated two hypotheses regarding the processing of double negation: (1) *Negativity Hypothesis (NH)*: negative operators affect the processing cost of a sentence additively; (2) *Monotonicity Hypothesis (MH)*: processing cost is additive in its entailment (⇑ vs. ⇓). We measured reaction times (RT) in a verification task, with sentences as in Table 1:

Table 1: Some Experimental Materials:	# of Neg.	Monotonicity
(a) Yoter me-chazi me-ha-'igulim hem kchulim/ zehubim 'More than half of the circles are blue/yellow.'	0	⇑
(b) Pachot me-chazi me-ha-'igulim hem kchulim/ zehubim '**Less** than half of the circles are blue/yellow.'	1	⇓
(c) Lo yoter me-chazi me-ha-'igulim hem kchulim/ zehubim '**Not** more than half of the circles are blue/yellow.'	1	⇓
(d) Lo pachot me-chazi me-ha-'igulim hem kchulim/ zehubim 'Not less than half of the circles are blue/yellow.'	2	⇑

If RT reflects processing cost, NH predicts that $RT_{(d)} > RT_{(c)}$ and $RT_{(b)} > RT_{(a)}$; MH predicts that $RT_{(c)} > RT_{(d)}$ and $RT_{(b)} > RT_{(a)}$.

THE HEBREW UNIVERSITY OF JERUSALEM

Experiment I pitted quantifier type against ±explicit negation (2×2, a-d in Table 1). We measured participants' error rate and RT to evaluate the processing difficulty. The prediction of MH was confirmed: $RT_{(c)}$(985ms) > $RT_{(d)}$(921ms); $RT_{(b)}$(897ms) > $RT_{(a)}$(805ms).



Experiments II, III added 2 syntactic configurations (e-f below, inducing a 2× 2×2 design) with in-lab participants (Hebrew), and via the web (English), By MH, different configurations lead carry the same predictions: $RT_{not\ more} \geq RT_{not\ less}$ (MH); $RT_{less...not} > RT_{more...not}$ (NH):

(e) Yoter me-chazi me-ha-'igulim hem lo kchulim/ zehubim 'More than half of the circles are **not** blue/yellow.'	1	⇓
(f) Pachot me-chazi me-ha-'igulim hem lo kchulim/ zehubim **'Less** than half of the circles are **not** blue/yellow.'	2	⇑

Though both (d) and (f) had a double negative, $RT_{(c)} > RT_{(d)}$ but $RT_{(f)} > RT_{(e)}$, as shown.

Conclusion The processing of double negation depends on the monotonicity and syntactic configuration of the negation(s). When the two negative operators form a constituent, the processing follows MH. However, when the two negative operators are separated, the processing cost accumulates as NH predicts.

Advisor: Prof. Yosef Grodzinsky

THE HEBREW
UNIVERSITY
OF JERUSALEM

Encoding of noxious stimuli by projection neurons of trigeminal nucleus caudalis in normal and pathological conditions

Ben Title

Trigeminal pain pathway involves the detection of noxious stimulus by trigeminal ganglion (TG) nociceptors, which innervate the orofacial and craniofacial areas. TG nociceptive fibers terminate in the brain stem trigeminal nucleus caudalis (TNc) onto second-order neurons comprised of local interneurons and projection neurons (PNs). PNs integrate nociceptive input from the periphery as well as the activity of the local interneurons, and transmit the information to higher brain regions. Although the anatomy of the trigeminal pain pathway is well characterized, an electrophysiological characterization is lacking. Specifically, how nociceptive input is encoded in TNc PNs and what is the role of the local interneurons in shaping their output are unknown. Furthermore, how pathological conditions such as inflammatory pain, affect TNc PNs properties and function are poorly understood.

We generated a mouse model, which enables the identification of PNs in TNc acute slices as well as specific activation of TG nociceptive axons using optogenetics. Behaviorally, we show that optogenetic activation of TG nociceptive fibers evokes withdrawal response. Physiologically, we demonstrate that TNc PNs differ in their responses to optogenetic stimulation of the nociceptive axons, with two prominent responses: (1) excitation and (2) excitation followed by inhibition. We further characterized TNc PNs in inflammatory condition in the trigeminal pathway using UV-keratitis model which results with corneal inflammation. TNc PNs in the inflammatory condition displayed similar distribution of responses to activation of the nociceptive axons. Surprisingly, PNs with excitatory response to nociceptive input displayed reduced excitability in the inflammatory condition. Corneal inflammation in the UV-keratitis model is known to result with increased excitability of TG nociceptive fibers, implying increased activation of TNc PNs. We suggest that TNc PNs reduce their excitability as a regulatory mechanism to reduce their activity and maintain homeostasis during inflammation.

Advisors: prof. Yosi Yarom & Prof. Alex Binshtok

THE HEBREW
UNIVERSITY
OF JERUSALEM

The cellular Landscape of the Aged and Alzheimer's Human Brains

Gilad Green

Alzheimer's Disease (AD) is an irreversible progressive age-associated neurodegenerative disease with no effective treatment. The focus of AD research has traditionally been on the damage to neuronal cells, yet, recently, studies from our labs and others have shown that multiple cell types in the brain are affected during disease progression. Specifically, new disease-associated states have been discovered across glial cell types, driving the need for a more comprehensive look at the changes in the entire cellular landscape of the brain with aging and AD. In this talk, we will present high-resolution cellular maps of two brain regions, the medial frontal cortex (MFC) and deep white matter (DWM), based on single nucleus RNA-sequencing (snRNA-seq) of aged individuals with diverse clinical and pathological characteristics. Comparing the cellular landscape across regions and disease traits, we uncover disease-associated states and regional cellular diversity.

Advisor: Dr. Naomi Habib

THE HEBREW
UNIVERSITY
OF JERUSALEM

Fixational drift is driven by diffusive dynamics in central neural circuitry

Nadav Ben Shushan

During fixation and between saccades, our eyes undergo diffusive random motion called fixational drift. The role of fixational drift in visual coding and inference has been debated in the past few decades, but the mechanisms that underlie this motion remained unknown. In particular, it has been unclear whether fixational drift arises from peripheral sources, or from central sources within the brain. Here we show that fixational drift is correlated with neural activity, and identify its origin in central neural circuitry within the oculomotor system.

We analyzed a large data set of ocular motoneuron (OMN) recordings in the rhesus monkey, alongside precise measurements of eye position, and found that most of the variance of fixational eye drifts must arise upstream of the OMNs. The diffusive statistics of the motion points to the oculomotor integrator, a memory circuit responsible for holding the eyes still between saccades, as a likely source of the motion. Theoretical modeling, constrained by the parameters of the primate oculomotor system, supports this hypothesis by accounting for the amplitude as well as the statistics of the motion. Thus, we propose that fixational ocular drift provides a direct observation of diffusive dynamics in a neural circuit responsible for storage of continuous parameter memory in persistent neural activity. The identification of a mechanistic origin for fixational drift is likely to advance the understanding of its role in visual processing and inference

Advisor: Burak Lab

THE HEBREW
UNIVERSITY
OF JERUSALEM

The end of neural crest cell production and emigration is regulated by retinoic acid-dependent BMP signaling

Dina Rekler

Production and emigration of neural crest cells is a transient process followed by the emergence of the definitive roof plate. The mechanisms regulating the end of neural crest ontogeny are poorly understood. Whereas early crest development is stimulated by mesoderm-derived retinoic acid, we report that the end of the neural crest period is regulated by retinoic acid synthesized in the dorsal neural tube. Inhibition of retinoic acid signaling in the neural tube prolongs the period of BMP responsiveness which normally ceases close to roof plate establishment in the dorsal midline. Consequently, neural crest production and emigration are extended well into the roof plate stage. Notably, although overall roof plate genes are expressed in the absence of retinoic acid signaling, roof plate and crest markers are co-expressed in single cells, this domain also contains dorsal interneurons and its cellular and molecular architecture are compromised. Together, our results demonstrate that neural tube-derived retinoic acid, via inhibition of BMP signaling, is an essential factor responsible for the end of neural crest generation and the proper segregation of dorsal neural lineages.

Advisor: Prof. Chaya Kalcheim

THE HEBREW
UNIVERSITY
OF JERUSALEM

Capacity and errors in classification of object manifolds

Uri Cohen

What makes a good object representation? How do object representations
change along biological or artificial hierarchies?

The collection of neural responses to different appearances of a single object is known as an *object manifold*. When those responses are complicated, the representation's utility for behavior is quantified by the ability to read-out relevant information from the neural population code. In this framework, we introduce a measure called *classification capacity* and argue it quantifies the goodness of a neural representation with respect to manifold classification. A theoretical analysis using tools from statistical physics allows us to relate this capacity to the geometry of object manifolds, thus augmenting the computational definition with an intuitive geometric perspective. Theory suggests that capacity is determined by a few measurable geometric quantities, such as extent and the number of axes of each manifold, along with the relations between manifolds.

Using deep convolutional neural networks trained on object classification as a "model animal" we show that capacity increases along the hierarchy of such networks. This increase can be traced to an orchestrated decrease in the dimensionality of the object manifolds created at each layer, as well as the ability of the hierarchy to decorrelate different manifolds. In those networks, different building-blocks have a predictable effect on the geometry of the object manifolds.

Finally, by allowing for noise in the representation we relate classification capacity to generalization error with respect to neural noise. This sheds light on the quality of noisy biological representations and suggests how to interpret experimental results of changes in neural representations.

Advisor: Prof. Haim Sompolinsky

THE HEBREW UNIVERSITY OF JERUSALEM

Inferring neural epigenetic changes in ancient human samples

Yoav Mathov

Novel techniques enable DNA extraction from ancient samples, including archaic humans such as Neanderthal and Denisovan. This provides an opportunity to study our recent past and examine evolutionary events which occurred in the genus Homo. Whereas gene regulatory changes are key drivers of evolutionary adaptations, gene activity patterns are difficult to infer from examination of ancient DNA (aDNA) sequences. Direct access to ancient RNA molecules is generally infeasible, but computational tools have been developed to reconstruct DNA methylation maps of ancient genomes.

While DNA methylation maps can be used as proxies to gene activity patterns, this epigenetic mark is strongly tissue-specific. Methylation patterns are more conserved across tissues than across species. Despite evidence of aDNA extraction from soft tissues such as skin and liver, bones remain the main source of aDNA samples. More specifically, as of today, no ancient DNA was extracted from the brain. Therefore, currently available ancient methylomes mostly provide information on the evolution of the skeletal system. Accordingly, the ability to infer non-bone-specific functions, such as neural processes, from ancient methylation maps, is limited.

Yet, DNA methylation in bones may carry some information on DNA methylation in other tissues. When a methylation change occurs in embryonic cells, in early developmental stages, we may see this change in all the tissues that will be developed from these embryonic cells. Such fundamental changes may allow inferring on neural-specific methylation patterns based on bone methylation.

In this talk I show that under certain evolutionary circumstances it is possible to identify such fundamental changes and hence to predict brain methylation from information on bones. Using parsimony, I showed that this task can be performed with up to 95% precision, based on data taken from modern tissues of primate species.

When applying this approach on archaic human, to detect human derived methylation changes, I found significant enrichment in genes related to brain function, nervous system development, neurons, and synapses. But also, such enrichment was found in higher functions such as cognition,

behavior and learning as well as in genes related to autism and mental retardation. Specifically, I found methylation changes in language-related genes such as FOXP2 and CNTNAP2, indicating that methylation changes might played a role in modern human brain evolution.

This approach allows for the first time to examine epigenetic changes in neural and other non-bone tissues in aDNA samples and opens an opportunity to investigate changes that occurred even in proximate human evolution, to better understand the role of brain evolution in adaptation and prosperity of Homo sapiens.

Advisor: Prof. Liran Carmel

THE HEBREW
UNIVERSITY
OF JERUSALEM

Maintenance of Bound or Independent Features in Visual Working Memory is Task-dependent

Ruoyi Cao

Over the last decade, seemingly conflicting results were obtained regarding the question of whether features of an object are stored separately, or bound together, in working memory (WM). Many of these studies are based on an implicit assumption about a default, or fixed, mode of working memory storage. However, according to recent findings about the functional property of WM, we proposed that anticipated memory probes used in a given experiment might actually determine the format in which information is maintained in WM. In order to test this flexible maintenance hypothesis, we recorded EEG while subjects performed a delayed-match-to-sample task with and without the requirement of maintaining bound features. In two experiments, we found significant differences in EEG signals recorded in central-parietal channels between the two conditions, providing reliable evidence for such flexible maintenance.

Advisor: Prof. Leon Deouell

THE HEBREW
UNIVERSITY
OF JERUSALEM

Reduced behavioral sensitivity to sound regularities in dyslexia is associated with reduced auditory-cortex sensitivity

Ayelet Gertsovski

A main characteristic of dyslexia is poor use of phonological categories. We now studied learning of new sound categories in dyslexia – behaviorally and neurally, using fMRI. Participants were asked to discriminate which of 2 serially-presented tones had a higher pitch. The task was administered in two protocols, with and without a reference frequency. The introduction of a reference facilitates the formation of pitch categories around it, and consequently increases typically developing (TD) individuals' frequency sensitivity. We found that in TDs, this learning was paralleled by a gradual decrease in activation of the auditory cortex. Among individuals with dyslexia (IDDs), both behavioral learning and auditory cortex adaptation to the repeated reference were reduced. IDDs' failed regularity detection was associated with larger activations in areas of the default-mode network. We propose that IDDs' reduced cortical adaptation associated with reduced learning of sound regularities underlie their impoverished representations of both speech and non-speech categories.

Advisor: Prof. Merav Ahissar

THE HEBREW
UNIVERSITY
OF JERUSALEM

Axonal spines on Inferior Olive neurons generate intrinsic regenerative currents when activated by synaptic input

Nora Vrieler

Dendritic spines have received a lot of attention in the context of understanding the structure and plasticity of neuronal processing, while spine heads on axons are relatively rarely studied even though they are not uncommon (Amaral 1978; Williams, Goldman-Rakic and Leranth 1992; Miller, Chiaia and Rhoades 1990). One example describes spines that are innervated by excitatory inputs on the axon hillock of cat Inferior Olive (IO) neurons (de Zeeuw et al. 1990). However, the functional significance of inputs arriving onto axonal spine heads has not yet been investigated.

In this work we describe a particular type of sub-threshold depolarizing events that occur spontaneously in IO neurons. These events are noteworthy for their large amplitude (up to 30mV) and fast rise-time (0.5 – 1.5ms), and are eliminated by the blockade of glutamatergic transmission. Furthermore, we show that these sub-threshold depolarizing events can be directly activated by optogenetic stimulation of specific groups of axons that innervate the IO. More interestingly, in any single neuron the amplitude distribution of these events reveals a distinct grouping, while the waveforms of amplitude-normalized events within a single neuron are identical. Using a NEURON simulation, we show that these properties are best explained by assuming that the events originate as intrinsic regenerative currents in axonal spine heads. This is further supported by demonstrating the existence of axonal spines in mouse IO neurons.

Taken together, these results suggest that IO neuron axons possess spines where intrinsic regenerative currents 'amplify' an incoming input. Thus, specific inputs are likely to carry a higher priority in activating an IO neuron's output, as they effectively bypass the rest of the neuron by activating the axon directly.

Advisor: prof. Yosi Yarom

THE HEBREW
UNIVERSITY
OF JERUSALEM

The blind leading the blind—how do we choose when no one knows anything?

Lotem Elber-Dorozko

Often, when choosing actions, it is challenging to predict their consequences: Is the left path the shorter one? Will this career choice help me become successful? Common practice in making such decisions is to rely on the choices of others. This can be useful both because others may know something that the subject does not know ('informational influences') and because our actions also have social consequences ('normative influence'). Often, both influences play a part in our decisions, so how can we measure their magnitudes in different contexts?

We used a novel paradigm to dissect informational and normative influences on decisions. In our paradigm, participants play a repeated two-alternative choice game with another player. Both players receive no feedback on their choices, the only available information is the choice of the other player. We manipulate informational influence: in one condition, informational influence leads the second player to choose similarly to the first (i.e., imitate), while in other conditions it leads her to choose the opposite action, or has no effect on imitation. Normative influence is similar in all conditions. We analyze data from several online experiments.

Surprisingly, we found that social influence biases participants away from imitation. Consistency in the choices of the other player increases subjects' tendency to choose consistently. We find a strong effect on imitation choices when informational and social influences lead in the same direction, and large heterogeneity in the imitation choices of subjects, partly related to gender, otherwise. Taken together, these results help predict people's behavior in scenarios where most of the given information is the choices of others.

Advisor: Prof. Yonatan Loewenstein

THE HEBREW
UNIVERSITY
OF JERUSALEM

Parkinson's Disease and Aging Related Microstructural Gradients in the Human Striatum Detected *in vivo* with Quantitative MRI

Elior Drori

The dorsal striatum, composed of the caudate nucleus and the putamen, is involved in motor control and goal-directed behavior. It is characterized by spatial heterogeneity of neurochemical environments and connectivity, showing gradients along its main axes. Changes in the striatal microstructure are associated with basal ganglia disease (e.g. Parkinson's disease (PD)) and aging-related declines in motor and cognition. Therefore, non-invasive quantification of the gradual changes that characterize the human striatal tissue has scientific and clinical importance. Quantitative MRI (qMRI) methods are sensitive to the microenvironment of the tissue, allowing for "in vivo histology" of the human brain. Here, we developed a non-invasive tool for quantifying structural heterogeneity along axes of the human striatum of individuals, using qMRI. We use this method to detect spatially dependent aging- and disease-related microstructural changes and provide evidence for the robustness of our method across datasets. First, we found qMRI gradients along axes of the putamen and caudate that were robust across subjects and two independent datasets. Second, these gradients showed laterality and aging-related changes that were replicated in both datasets. Third, we investigated the biophysical sources of spatial change in the aging striatum, using several qMRI parameters, associated with myelin and lipid content (R1), the non-water content of the tissue (MTV) and the iron concentration (R2*). We found distinct profiles of spatial change in the striatum for each of these parameters, as well as distinct associated agingrelated changes. Last, in PD patients we found changes in the putamen gradients that correlated with the patient's clinical motor symptoms evaluation and the striatal dopamine uptake, measured invasively using SPECT. Our findings suggest that different parameters of qMRI reveal distinct biological sources involved in the spatial heterogeneity of the striatal tissue in vivo. Moreover, aging-related changes involving these sources manifest differently in the striatum. Quantification of striatal gradients in the living human brain proves useful for detecting structural abnormalities that characterize and relate to the symptoms of basal ganglia diseases such as Parkinson's disease.

Advisor: Prof. Aviv Mezer

THE HEBREW
UNIVERSITY
OF JERUSALEM

What is an episode in episodic memory?

Aya Ben-Yakov

Real life experience is continuous, yet when we reminisce about the past, we typically remember it as discrete episodes. How is continuous experience segmented and registered to long-term memory as separate events? Leading theories suggest that episodic elements are encoded independently of one another – each bound to the current context, with no direct link between adjacent elements. Findings of hippocampal encoding-related activity at event boundaries (moments of transition from one event to the next) led to formulation of new models. These suggest event boundaries trigger the encoding of the preceding event as a cohesive unit. I will discuss past and future research geared at identifying the basic building block of episodic memory, asking whether elements are encoded independently, or whether episodes are encoded as cohesive units. Contrary to our predictions, in a recent study we find evidence supporting the former: when incorporating surprising elements in ordinary events, we find that surprise increases memory for the surprising element alone, leaving other episodic elements unaffected.

THE HEBREW
UNIVERSITY
OF JERUSALEM

Poster abstract

THE HEBREW UNIVERSITY OF JERUSALEM

Rapid Responses to Auditory Frequency Change, Its Magnitude and Direction – from Brain to Action

Amos David Boasson, Gal Vishne, Leon Deouell, Roni Granot

Background Auditory frequency change [FC] may convey to perceivers potentially crucial environmental cues. Short-latency behavioral responses to FC have been documented in animals and humans. Our research-line explores swift (albeit at times covert) effects of FC and its parameters on human motor action, seeking insight on where this information may be relayed into motor commands.

Previously we employed paradigms of finger tapping to isochronous beeps, monitoring negative mean asynchrony [NMA], electromyography and finger acceleration; beep-sequences presented task-irrelevant increments/decrements, in frequency /intensity. Presentation of FC elicited aug-mented NMA, revealing a 'melodic' asymmetry: 'tap-earliness' was yet more enhanced following Rise (thus no mere surprise effect). Physiological data detected Rise's effect-onset at ~160 ms post-FC; Fall impacted action significantly later. Some queries were left open.

Aims The present study explored FC's effect on behavior in a motor act evoked in response to FC, at high timing uncertainty of motion-onset (in lieu of actions pre-planned by regularly paced auditory information as in our tapping paradigm). Aiming to enhance insight of when and where auditory-to-motor mediation occurs, we now added brain activity to the indices monitored .

Methods In a demanding reaction-time [RT] task, 32 musicians heard rapid sequences of single-frequency pure-tone beeps (rate 8 Hz, jittered). At semi-randomized intervals (average rate 1 Hz) FCs at varying magnitude and direction were presented. A button-press was required upon perceiving any FC; superior execution was rewarded. RTs were recorded along with brain activity (EEG), brainstem activity (ABR), muscle activity (EMG), and finger acceleration.

Results RTs were rapid (mean 203 ms). Muscle response began as early as 70 ms post trial onset. Change magnitude affected behavior already at action onset: Bigger steps yielded earlier action. Change direction affected action significantly as well, but to a lesser degree: Fall yielded earlier action. Brain activity was found to decode FC, including its magnitude and direction, already at brainstem and through the following components.

Conclusion Detailed FC detection early up the auditory pathways elicited (in musicians) ultra-early action response. This suggests early 'decisions' relay finely-processed auditory information to the motor system at the primary auditory cortex level, or even sub-cortically.

Implications Bottom-up and top-down processes meet at 'low' levels, activating auditory-to-motor relays; enabling rapid responses to relevant FC information, such primal routes may act regularly, though covertly, perhaps forming a 'low-level' facet of music perception.

Advisor: Prof. Leon Deouell

THE HEBREW
UNIVERSITY
OF JERUSALEM

Navigating by The Stars: The Role of Astrocytes in Spatial Cognition

Adi Doron

In recent years, groundbreaking research revealed many surprising roles for astrocytes in modulating neuronal activity and even behavior. While astrocytes in cortical areas were shown to respond to specific sensory stimuli, their activity in awake mice performing a multisensory cognitive task has not been studied. To investigate the functional role of astrocytes, we used 2-photon calcium imaging in dorsal CA1 of mice running in a virtual reality apparatus. We imaged dozens of astrocytes as mice ran in a familiar circular virtual maze, in which a reward was given in a constant location, and examined whether astrocytes independently encode spatial and non-spatial features of the environment. Astrocytes did not have bell-shaped tuning curves, typical to neuronal place cells, but rather appeared to increase their activity as they approached the previously learnt reward location. Using machine learning, we were able to successfully decode the mouse location from the astrocyte activity alone. We next imaged the same population of astrocytes while the mice were introduced to a novel virtual environment differing in visual and tactile cues. Notably, the astrocytic activity was no longer modulated by the location, suggesting that the elevation of activity towards a rewarding location requires familiarity with the environment. Our results shed light on the computational capabilities of astrocytes, their role in learning a new environment until it becomes familiar, and their contribution to cognitive functions.

Advisor: Prof. Inbal Goshen

THE HEBREW
UNIVERSITY
OF JERUSALEM

Parkinson's Disease and Aging Related Microstructural Gradients in the Human Striatum Detected in vivo with Quantitative MRI

Elior Drori

The dorsal striatum, composed of the caudate nucleus and the putamen, is involved in motor control and goal-directed behavior. It is characterized by spatial heterogeneity of neurochemical environments and connectivity, showing gradients along its main axes. Changes in the striatal microstructure are associated with basal ganglia disease (e.g. Parkinson's disease (PD)) and aging-related declines in motor and cognition. Therefore, non-invasive quantification of the gradual changes that characterize the human striatal tissue has scientific and clinical importance. Quantitative MRI (qMRI) methods are sensitive to the microenvironment of the tissue, allowing for "in vivo histology" of the human brain. Here, we developed a non-invasive tool for quantifying structural heterogeneity along axes of the human striatum of individuals, using qMRI. We use this method to detect spatially dependent aging- and disease-related microstructural changes and provide evidence for the robustness of our method across datasets.

First, we found qMRI gradients along axes of the putamen and caudate that were robust across subjects and two independent datasets. Second, these gradients showed laterality and aging-related changes that were replicated in both datasets. Third, we investigated the biophysical sources of spatial change in the aging striatum, using several qMRI parameters, associated with myelin and lipid content (R1), the non-water content of the tissue (MTV) and the iron concentration (R2*). We found distinct profiles of spatial change in the striatum for each of these parameters, as well as distinct associated agingrelated changes. Last, in PD patients we found changes in the putamen gradients that correlated with the patient's clinical motor symptoms evaluation and the striatal dopamine uptake, measured invasively using SPECT.

Our findings suggest that different parameters of qMRI reveal distinct biological sources involved in the spatial heterogeneity of the striatal tissue in vivo. Moreover, aging-related changes involving these sources manifest differently in the striatum. Quantification of striatal gradients in the living human brain proves useful for detecting structural abnormalities that characterize and relate to the symptoms of basal ganglia diseases such as Parkinson's disease.

Advisor: Prof. Aviv Mezer

THE HEBREW UNIVERSITY OF JERUSALEM

Implementing the Information Bottleneck approach for RNA-Seq analysis

Sima Dubnov, Hermona Soreq and Naftali Tishby

The world's population is growing older due to improving health care and life conditions, increasing the prevalence of aging-associated diseases that involve dementia. Nowadays more than 1 in 9 people older than 65 develop Alzheimer's Disease (AD), and this ratio will predictably grow in coming years. AD diagnosis is still largely limited to cognitive and behavioral tests, meaning that intervention is only possible at the advanced AD stages, which greatly reduces the prospects of disease-changing therapeutics. Thus, reliable approaches should be pursued to allow earlier AD diagnosis.

Transcriptomic profiling based on RNA-Seq is a promising diagnostic approach, since it robustly reflects the current state of the tested tissue. RNA-seq quantifies the copy numbers of RNA transcripts of each gene expressed in a processed sample, resulting in big data which requires proper analysis and compression. The selected data compression tools depend on the ultimate goal of the analysis. For example, many genes are not affected by Alzheimer's, so they are irrelevant for AD diagnosis and thus represent noise. However, the more data is filtered out or squeezed, the more information is lost about the disease.

The **Information Bottleneck** (IB) method introduced by Naftali Tishby (Tishby et al, 1999) is designed to achieve the optimal trade-off between accuracy and complexity in compressing big data. The IB algorithm reduces the data dimensionality by finding a compressed representation that preserves the maximum information about an external variable that is being predicted. The compression is achieved by merging datapoints that carry similar information about the predicted variable, thus forming representative clusters.

The IB approach might prove to be particularly useful in RNA-Seq data analysis for several reasons. First of all, the IB-generated clusters have a direct application in hypothesis testing: the compressed representation of data achieved by IB optimizes the distinguishability power of the likelihood-ratio test discriminating between different realizations of the predicted variable. Hence, the reduced representation of the original data formed by IB offers optimal discriminability in prediction of this external variable of interest at a given level of accuracy. Such statistical justification of specific clusters is of major importance when choosing relevant transcripts for Alzheimer's Disease diagnosis, which

provides IB with a great advantage over other clustering methods in RNA-Seq analysis. Furthermore, the IB algorithm represents a novel universal clustering method which does not require any probabilistic assumptions about the distribution of the input variable, unlike other common clustering techniques that often assume Gaussianity. Since gene expression distribution is often non-Gaussian, the IB approach is advantageous in analyzing RNA-Seq data.

In this poster I will present some preliminary results based on application of the IB algorithm in RNA-Seq analysis. In particular, I have analyzed the RUSH RNA-Seq dataset of postmortem brain samples from Nucleus Accumbens of elderly demented patients and healthy age-matched controls (n=190). The results demonstrate that the IB clusters represent distinct molecular processes which are known to be affected by the pathology.

THE HEBREW
UNIVERSITY
OF JERUSALEM

References:

N. Tishby, F. C. Pereira, and W. Bialek. The Information Bottleneck method. In *Proceedings of the 37th Annual Allerton Conference on Communication, Control and Computing*, 1999.

Advisors of Sima Dubnov: Hermona Soreq, Naftali Tishby

THE HEBREW
UNIVERSITY
OF JERUSALEM

Uncovering the specificity of quantitative MRI to different molecular forms of iron in the brain

Shir Filo, Rona Shaharabani, Hanan Schoffman, Daniel Bar Hanin, Masha Adam, Naomi Habib, Tal Shahar, Aviv Mezer.

The main iron compounds, ferritin and transferrin, are distributed heterogeneously across the brain and are often implicated in neurodegenerative diseases. While quantitative MRI (qMRI) parameters such as R1 and R2* have been linked to brain tissue's microstructure, non-invasive discrimination between iron forms still remains a challenge. Here we present a new MR-relaxivity approach for increasing the sensitivity of MRI to different molecular forms of iron. First, we confirm in-vitro that different iron-bound proteins induce different relaxivities, which can be estimated with MRI. Remarkably, when examining the qMRI measurements of the R1-R2* interdependencies (R1-R2* slopes) we expose the intrinsic ferromagnetic properties of different iron forms. In the human brain we show that the in-vivo iron relaxivity, estimated by the R1-R2* slopes, provides a new MRI contrast. This contrast proves useful for enhancing the distinction between tumor tissue and non-pathological tissue. We further demonstrate that this new contrast allows to detect biological properties inaccessible by conventional MRI approaches. We confirmed this by comparing our in-vivo MRI contrast to RNA-sequencing and proteomics of resected tumor tissue. This unique in-vivo to ex-vivo strategy, along with group-level analysis on healthy subjects, are used to establish the sensitivity of the R1-R2* slopes to molecular iron forms in the brain. The R1-R2* slopes contrast allowed us to predict the inhomogeneous distribution of iron-binding proteins due to aging and across the brain, and to reveal differences in iron hemostasis between tumor tissues.

Advisor: Prof. Aviv Mezer

THE HEBREW
UNIVERSITY
OF JERUSALEM

Dichotomous Activity and Function of Neurons with Low and High Frequency Discharge in the External Globus Pallidus

Shiran Katabi, Avital Adler, Marc Deffains and Hagai Bergman

Today, there is no debate regarding the existence of at least two neuronal populations in the non-human primate (NHP) external globus pallidus (GPe): the low and high frequency discharge (LFD and HFD) neurons. Nevertheless, almost all NHP studies on the role of the GPe in basal ganglia (BG) functions neglect the functional importance of the LFD neurons. To fill this gap, we examined the discharge features of these two distinct neuronal subpopulations recorded in four monkeys engaged in a classical conditioning task. We found that LFD neurons tended to burst with a characteristic accelerating-decelerating burst pattern, whereas HFD neurons tended to pause. Moreover, the LFD and HFD neurons encoded cue salience and valence, respectively. Finally, LFD neurons showed correlated activity, while HFD neurons did not. Overall, this study demonstrates that the dichotomic organization of the NHP GPe is most likely critical for the implantation of normal BG functions and computations.

Advisor: Prof. Hagai Bergman

THE HEBREW UNIVERSITY OF JERUSALEM

Ventrolateral Striatum (VLS) Centric Neural Circuits Select Specific Orofacial Actions in Context-Dependent Manner

David Lipton

The Striatum is a brain region hub integrating sensorimotor drive with selective reinforcement to select appropriate action repertoires. Habits, compulsions, and addictions rely on plasticity within striatal circuits. The central question of my project is: **Within the broader ventrolateral striatum (VLS) orofacial and upper-limb striatal territory and relevant inter-connected basal ganglia subregions, how are individual actions relevant to these body parts encoded?** Is each orofacial action represented by a topographically defined subregion of the VLS? Or, at the other extreme, does the VLS as a whole broadly elevate the probability of a wide array of orofacial action, with the selection of the specific action chosen determined by other factors such as the contextual cues (i.e. stimuli) present in the animal's environment? I show here that both topographical location within the striatum and contextual information present in an animal's environment converge within the striatum to influence the distinct action produced by VLS direct-pathway neurons. Furthermore, activation of VLS indirect pathway neurons inhibits orofacial stereotypies, while leaving other types of behavioral expression unaffected. I then ask how the basal ganglia subregion directly downstream of VLS striatum, the SNR, conveys information from VLS-initiated neural activity to select individual orofacial actions. Here, preliminary data indicate that individual actions become more stereotyped and topographically encoded in the SNR, one step 'downstream' from striatum, and one step closer to motor output. Finally, I ask how cortical inputs to the VLS influence choice of action: I hypothesize that sensorimotor information pertaining to the current state/context the animal is in are represented in corticostriatal input to the striatum, and that these projections function to elevate striatal activity, preferentially in direct-pathway neurons, generating distinct behaviors that are appropriate to the given state/context. Surprisingly, despite stimulating corticostriatal inputs to the VLS under many different conditions, I have not been able to observe an effect of VLS-input stimulation on influencing behavior. I am currently continuing to investigate the role of these inputs in modulating neuronal activity in VLS-resident circuits and driving behavior.

Professor: Ami Citri

THE HEBREW
UNIVERSITY
OF JERUSALEM

Anatomical architecture of distinct feedback circuits to the Auditory cortex

Claudia Maggi

Cortical processing depends on both bottom-up and top-down inputs. Top-down inputs come from various sources but neither their anatomy nor function are well understood. Here, we studied the connectivity logic of two regions feeding back to primary auditory cortex (A1) - the contralateral A1 (A1_contra) and orbitofrontal cortex (OFC). Both regions are known to be reciprocally connected with AC and to respond robustly to auditory cues.

We asked whether feedback connectivity from AC_contra to A1 and from OFC to A1 is primarily a reciprocal monosynaptic input connection. Specifically, we asked to what extent A1_contra→A1 or OFC→A1 neurons receive their own inputs from A1 itself (thus forming a monosynaptic reciprocal circuit). To this end, we used a variant method of the rabies-mediated trans-synaptic tracing tool, called cTRIO (cre-dependent Tracing Relationships of Inputs and Outputs). Using cTRIO, we traced the presynaptic partners of A1_contra→A1 or OFC→A1 neurons.

We found that A1_contra→A1 neurons receive considerable amounts of their inputs from A1 itself while OFC→A1 neurons do not. This connectivity logic suggests distinct computations for the two distinct feedback connections. On the one hand, A1_contra→A1 transfers low-level auditory information among the cortices. On the other hand, the OFC→A1 feedback is likely involved in non-auditory computations like, for example, modulating cortical responses based on context.

Advisor: Prof. Adi Mizrahi

THE HEBREW
UNIVERSITY
OF JERUSALEM

Cortical plasticity following auditory perceptual learning

Ido Maor and Benne Praegel

Auditory learning related plasticity, has been mainly studied in the primary auditory cortex (A1), the first cortical station in the hierarchical flow of information along the auditory pathway. How the learned information is represented in neural circuits at different fields of the cortical hierarchy and how this may contribute to learning remain open questions.

We studied the neural correlates of auditory perceptual learning in the primary auditory cortex, as well as in higher cortical regions. We used the newly developed high-density microelectrode arrays- the Neuropixels to record single unit spiking activity from multiple neurons and cortical regions, simultaneously. Specifically, we measured the response properties of neurons from A1, temporal association cortex (TeA) and orbitofrontal cortex (OFC) of naïve mice vs expert mice who underwent auditory perceptual learning of complex sounds. We will describe preliminary anlayses of basic sound features as they change along the hierarchy and after learning.

Advisor: Prof. Adi Mizrahi

THE HEBREW UNIVERSITY OF JERUSALEM

Recent to Remote Memory Activity and Connectivity

Ron Refaeli, Dr. Tirzah Kreizel and Prof. Inbal Goshen

"We are nothing more than the sum of our memories"

When a memory is acquired, a group of neurons with high activity levels during learning are allocated to support it. Some of these neurons will later participate in the recall of this memory. Their activity during the *acquisition* of a memory is necessary for recall of recent (days post acquisition) and even remote (a month and more post acquisition) memories.

Recent memory involves relatively fast processes that take place during the first hours to days following learning. Remote memories, however, are consolidated over much longer time scales, in a yet not well-defined processes termed together 'systems consolidation'. This process involves changes in multiple brain regions that enable the persistence of the memory.
In this research we targeted the transition of a memory from recent to remote recall, in order to find missing links between these memory stages. For that purpose, we tagged a first cFos positive cells using genetic manipulation, and a second group of cFos positive cells using immunohistochemistry, within the same mouse, thus allowing comparison of the two populations in each animal.
First, we show that neuronal activation throughout different stages in memory consolidation and reconsolidation is consistent in the hippocampus, but not in other memory related brain areas, compared to the acquisition of a memory.
Secondly, during the transition from recent to remote recall, several brain structures maintain fixed ensembles, not necessarily similar to the acquisition. Furthermore, hyper activation of hippocampal astrocytes during memory acquisition, known to enhance recent memory, increase the percentage of CA1 reactivated cells between recent and remote recall.

In order to define whether the ensembles supporting remote memory are selected based on their connectivity and if they differ from the ensembles supporting recent memory, we marked cells in the CA1 based on their projection target. We found that the transition from recent to remote memory does include recruitment of projection based sub-population; CA1 to ACC projecting cells are more likely to be activated during remote recall than during recent recall or acquisition. Additionally, hyper activation of hippocampal astrocytes during an acquisition of a memory, also increases the activation of the CA1 to ACC projecting cells during recent but not remote recall.

Lastly, analyzing projections of active cells from the CA1 during different stages of memory consolidation, using full brain reconstruction, revealed that as time progresses, the CA1 to ACC projections ratio increases, compared to other areas monosynaptic connected to the CA1, such us the supra mammillary bodies or Nucleus Accumbens.

Advisor: prof. Goshen

THE HEBREW UNIVERSITY OF JERUSALEM

The processing of double negation

I-An Tan and Nir Segal

Overview This study aims to better understand the nature of negation processing cost. We know that sentences with overt (e.g., *no*, *not*) or covert (e.g., *less*, *few*) negative markers take more time to process than their affirmative counterparts (Wason 1959; Deschamps et al., 2015.) A common property for both kinds of markers is that they create a Downward Entailing (⇓) environment (you did*n't eat an apple*→you did*n't eat a green apple*), as opposed to negationless sentences which are Upward Entailing (⇑) (you *ate a green apple*→you *are an apple*). Two negative markers also induce an Upward Entailing environment (⇑).

Is processing cost tied to negation, or to the entailment properties of sentences (Monotonicity)? We formulated two hypotheses regarding the processing of double negation: (1) *Negativity Hypothesis (NH)*: negative operators affect the processing cost of a sentence additively; (2) *Monotonicity Hypothesis (MH)*: processing cost is additive in its entailment (⇑ vs. ⇓). We measured reaction times (RT) in a verification task, with sentences as in Table 1:

Table 1: Some Experimental Materials:	# of Neg.	Monotonicity
(a) Yoter me-chazi me-ha-'igulim hem kchulim/ zehubim 'More than half of the circles are blue/yellow.'	0	⇑
(b) Pachot me-chazi me-ha-'igulim hem kchulim/ zehubim '**Less** than half of the circles are blue/yellow.'	1	⇓
(c) Lo yoter me-chazi me-ha-'igulim hem kchulim/ zehubim '**Not** more than half of the circles are blue/yellow.'	1	⇓
(d) Lo pachot me-chazi me-ha-'igulim hem kchulim/ zehubim **'Not less** than half of the circles are blue/yellow.'	2	⇑

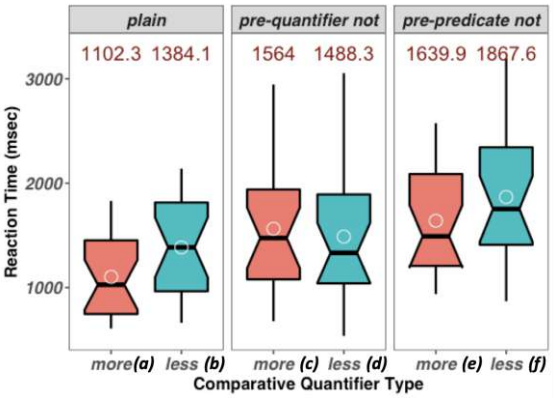
If RT reflects processing cost, NH predicts that $RT_{(d)} > RT_{(c)}$ and $RT_{(b)} > RT_{(a)}$; MH predicts that $RT_{(c)} > RT_{(d)}$ and $RT_{(b)} > RT_{(a)}$.

THE HEBREW UNIVERSITY OF JERUSALEM

Experiment I pitted quantifier type against ±explicit negation (2×2, a-d in Table 1). We measured participants' error rate and RT to evaluate the processing difficulty. The prediction of MH was confirmed: $RT_{(c)}$(985ms) > $RT_{(d)}$(921ms); $RT_{(b)}$(897ms) > $RT_{(a)}$(805ms).

Experiments II, III added 2 syntactic configurations (e-f below, inducing a 2×2×2 design) with in-lab participants (Hebrew), and via the web (English), By MH, different configurations lead carry the same predictions: $RT_{not\ more} \geq RT_{not\ less}$ (MH); $RT_{less...not} > RT_{more...not}$ (NH):

(e) Yoter me-chazi me-ha-'igulim hem lo kchulim/ zehubim 'More than half of the circles are **not** blue/yellow.'	1	⇓
(f) Pachot me-chazi me-ha-'igulim hem lo kchulim/ zehubim **'Less** than half of the circles are **not** blue/yellow.'	2	⇑



Though both (d) and (f) had a double negative, $RT_{(c)} > RT_{(d)}$ but $RT_{(f)} > RT_{(e)}$, as shown.

Conclusion The processing of double negation depends on the monotonicity and syntactic configuration of the negation(s). When the two negative operators form a constituent, the processing follows MH. However, when the two negative operators are separated, the processing cost accumulates as NH predicts.

Advisor: Prof. Yosef Grodzinsky

THE HEBREW UNIVERSITY OF JERUSALEM

A phantom system for evaluating the effect of lipid and iron composition on qMRI parameters

Rona Shaharabani

Neurodegenerative diseases such as Alzheimer's, Parkinson's, and Multiple sclerosis are often linked to abnormal changes in lipids and iron. Both lipid and iron contents have been shown to have a strong effect on magnetic resonance imaging (MRI) signal[1,2]. Nevertheless, it's still a major challenge to identify and quantify the contributions of specific molecular compounds to the MRI signal. Specifically, it is hard to distinguish whether changes in qMRI measurements (such as the relaxation rate, R2*) result from changes in iron paramagnetic properties or alterations in the lipid content[2–4]. For example, in the human brain, where iron and lipid content changes are correlated[4], it may be rather difficult to distinguish between the contribution of each component separately.

We had previously demonstrated that our in vitro system can estimate multiple qMRI with high reproducibility[1]. Here, we examine the combined effects of the iron and lipid compositions on quantitative MRI parameters using this in vitro system. With our in vitro system, we control the amount of lipids, their type, and the iron concentration hence, we can identify their specific contribution.

In this study, we focus on the relaxation rate R2* which is known to be a marker for brain iron. Indeed. As expected, R2* was affected by iron concentration, with increased concentrations of Fe^{2+} exhibiting greater R2* in the presence of different lipid types. In addition, we found that R2* values are also highly dependent on the lipid-water fraction.

We propose that our in vitro system, in which we control both the lipid type and iron content will allow us to better understand and model the biophysical sources of qMRI parameters and improve their use as biomarkers for assessing brain changes.

1. Shtangel, O. & Mezer, A. A. *NMR Biomed.* **33**, (2020).
2. Filo, S. *et al. Nat. Commun.* **10**, 3403 (2019).
3. Mezer, A. *et al. Nat. Med.* **19**, 1667–1672 (2013).
4. Stüber, C. *et al. Neuroimage* **93**, 95–106 (2014).
5. Möller, H. E. *et al. Trends in Neurosciences* **42**, 384–401 (2019).

Advisor: Prof. Aviv Mezer

THE HEBREW UNIVERSITY OF JERUSALEM

Subcortical and cortical tracking of complex sound envelopes in challenging listening conditions

Souffi S.[1, 2], Varnet L. [3], Huetz C. [1,2], Edeline J.-M.* [1,2]

1 Paris-Saclay Institute of Neuroscience (Neuro-PSI), Department Integrative and Computational Neuroscience, UMR CNRS 9197.

2 Université Paris-Sud, Bâtiment 446, 91405 Orsay cedex, France.

3 Laboratoire des systèmes perceptifs, UMR CNRS 8248, Département d'Etudes Cognitives, Ecole Normale Supérieure, Université Paris Sciences & Lettres, Paris, France.

In humans, speech signals are characterized by rhythmic stream of amplitude and frequency fluctuations that convey phoneme, syllable, word, and phrase information (Rosen 1992). It is known for several decades that the modulations of slow temporal envelope are essential cues for speech perception (Drullman et al., 1994; Shannon et al., 1995; Zeng et al., 2005): even in challenging conditions, the human auditory system has the capacity to process highly degraded speech as long as the temporal envelope modulations below 20 Hz are preserved (Drullman et al., 1994a, b; Shannon et al., 1995). In animals, several electrophysiological studies have reported that cortical and collicular neurons can synchronize their responses to speech or to animal communication sounds (Wang et al., 1995; Suta et al., 2003; Wallace et al., 2005; Woolley et al., 2006; Wallace & Palmer, 2009; Grimsley et al., 2011, 2012; Rode et al., 2013; Abrams et al., 2017). Here, we recorded neuronal responses in the cochlear nucleus, inferior colliculus, thalamus, primary and secondary auditory cortex at presentation to four conspecific vocalizations presented in quiet, using three tone-vocoders and in addition of two types of noise (a stationary and chorus noise) in anesthetized guinea pigs. We performed cross-correlations with both filtered envelopes and PSTHs in four amplitude modulation (AM) ranges from very low to high ranges and looked for relationships between the neuronal discrimination performance (quantified with the mutual information) and the envelope tracking ability.

We found that subcortical and cortical neurons track the envelope in the low and very low AM ranges respectively, with relatively high degree of fidelity in original and degraded conditions, suggesting that the auditory system maintains a robust temporal code from the cochlear nucleus to the auditory cortex. Furthermore, we revealed that the between-stimuli envelope differences explained the changes in neuronal discrimination at the subcortical and cortical levels. Our data, together with previous human and animal results, provide converging lines of evidence that tracking the stimulus envelope is an ancestral property strongly preserved through evolution and can be viewed as an acoustic marker for predicting the changes of discriminative abilities in many situations in the whole auditory system.

THE HEBREW
UNIVERSITY
OF JERUSALEM

Encoding of noxious stimuli by projection neurons of trigeminal nucleus caudalis in normal and pathological conditions

Ben Title

Trigeminal pain pathway involves the detection of noxious stimulus by trigeminal ganglion (TG) nociceptors, which innervate the orofacial and craniofacial areas. TG nociceptive fibers terminate in the brain stem trigeminal nucleus caudalis (TNc) onto second-order neurons comprised of local interneurons and projection neurons (PNs). PNs integrate nociceptive input from the periphery as well as the activity of the local interneurons, and transmit the information to higher brain regions. Although the anatomy of the trigeminal pain pathway is well characterized, an electrophysiological characterization is lacking. Specifically, how nociceptive input is encoded in TNc PNs and what is the role of the local interneurons in shaping their output are unknown. Furthermore, how pathological conditions such as inflammatory pain, affect TNc PNs properties and function are poorly understood.

We generated a mouse model, which enables the identification of PNs in TNc acute slices as well as specific activation of TG nociceptive axons using optogenetics. Behaviorally, we show that optogenetic activation of TG nociceptive fibers evokes withdrawal response. Physiologically, we demonstrate that TNc PNs differ in their responses to optogenetic stimulation of the nociceptive axons, with two prominent responses: (1) excitation and (2) excitation followed by inhibition. We further characterized TNc PNs in inflammatory condition in the trigeminal pathway using UV-keratitis model which results with corneal inflammation. TNc PNs in the inflammatory condition displayed similar distribution of responses to activation of the nociceptive axons. Surprisingly, PNs with excitatory response to nociceptive input displayed reduced excitability in the inflammatory condition. Corneal inflammation in the UV-keratitis model is known to result with increased excitability of TG nociceptive fibers, implying increased activation of TNc PNs. We suggest that TNc PNs reduce their excitability as a regulatory mechanism to reduce their activity and maintain homeostasis during inflammation.

Advisors: prof. Yosi Yarom & Prof. Alex Binshtok

THE HEBREW
UNIVERSITY
OF JERUSALEM

Roles of stress-related small RNA regulators in Alzheimer's disease

Katarzyna Winek, Nimrod Madrer, Gürsel Caliskan, David S Greenberg, Michael T Heneka, David Bennett and Hermona Soreq

Currently approved medications of Alzheimer's disease (AD) only alleviate disease symptoms, and ample scientific resources seek druggable targets. Recent rodent studies demonstrated that gamma oscillations (neuronal rhythms in 20-50 Hz frequency) limit amyloid levels and AD damage, inducing phagocytic responses of microglia (Iaccarino *et al.* 2016). Further, cholinergic-mediated hippocampal gamma rhythms decline under stress, but it is unknown if this decline causally accelerates AD damage. To challenge the hypothesis that specific stress-related small RNA regulators including microRNAs (miRNAs) and transfer RNA fragments (tRFs) may impact the gamma oscillations, we applied established stress paradigms in a rat model. Stressed rats showed reduced gamma oscillations in the left hippocampus and small RNA-sequencing revealed marked changes in multiple tRF levels in the ventral and dorsal parts of the hippocampus (30 differentially expressed tRFs in the ventral hippocampus, derived mostly from the 3' of tRNAs and 19 differentially tRFs in the dorsal part, mostly i-tRFs). In comparison, we found relatively few changes in the expression of hippocampal miRNAs (limited to stress-induced increases in miR-29b-3p, -29c-3p and -137-3p and decreases in miR-135a-3p and -320-3p), indicating larger potential functional relevance of tRFs. To seek tRF changes in the human AD brain, we analyzed 181 and 197 hypothalamus and nucleus accumbens tissues of donors enrolled to the Religious Orders Study (ROS) and Memory and Aging Project (MAP) from Rush University, Chicago, USA (Bennett et al., 2005), where we identified further differences in tRF levels (16 differentially expressed molecules, enriched in i-tRFs). Characterizing and modulating the stress-suppressed gamma oscillations-related small RNA changes may lead to a novel approach to reverse the AD-induced processes in deep cholinergic nuclei, opening new diagnostic and therapeutic venues.

Advisor: Prof. Hermona Soreq

THE HEBREW
UNIVERSITY
OF JERUSALEM

Category learning of sounds in mice – a behavioral study

Or Yudco

To make sense of highly complex environments, the brain uses categorization as a reduction mechanism. In categorization, different stimuli or experiences are grouped together into a single percept by ignoring individual differences while linking together common features. This mechanism allows to identify new stimuli that was never encountered before as belonging to a given learned category. Most categories must be learned through experience, but how the brain learns to categorize is not well understood. Using an automated learning platform, we trained mice on a variety of protocols to discriminate between rising and falling frequency modulated (FM) sweeps. By testing how mice behave in response to novel stimuli we found that mice use the frequency content of the stimulus to categorize among FM stimuli. Our work serves as a substrate to current electrophysiological measurements that we use to study the neural substrate underlying categorizations.

Advisor: prof. Adi Mizrahi

THE HEBREW
UNIVERSITY
OF JERUSALEM

Developing sex-specific cholinergic cellular models for studying the superior temporal gyrus-related language processing damage in Alzheimer's brains

Tamara Zorbaz, Nimrod Madrer, Muslum Gok, Katarzyna Winek, David A. Bennett, Hermona Soreq

Alzheimer's disease (AD) is a well-known neurodegenerative disease and the most common cause of dementia. Cholinergic neurons degenerate early in the disease process and decline of the brain's cholinergic network plays an important role in both the initiation and propagation of AD. Correspondingly, multiple studies reported increased risk of dementia in cognitively healthy aged patients exposed to prolonged treatment with anticholinergic drugs. Decreased neurotransmission via acetylcholine (ACh) is accompanied by declined levels of proteins involved in ACh production and by changes in its degradation enzymes (acetylcholinesterase (AChE), butyrylcholinesterase). Therefore, AChE inhibitors (AChEI) serve as symptomatic treatment to increase the cholinergic tone and cognitive function. Women are significantly more sensitive to AChEI treatment in AD, but the origin(s) of these sex-related differences remained largely unexplained. For all of these reasons, we wish to comparatively study the impact of (anti)cholinergic drugs on man- and woman-originated neuronal cell lines along cholinergic differentiation.

The study began by investigating the expression of cholinergic genes in the superior temporal gyrus (STG) brain samples collected from healthy aging men and women donors compared to Alzheimer disease patients; STG is involved in language processing and social recognition, both deeply affected cognitive functions in AD. Next, sex-specific effects will be studied by comparing the impact of different (anti)cholinergic drugs on two neuroblastoma cell lines, female SH-SY5Y and male LAN-5 cells, after cholinergic differentiation. Preliminary results showed distinct expression patterns of ACh receptors and AChE and BChE transcripts and alternative splicing thereof in the AD brain, as well as different sex-characteristic impact of differentiation factors (CNTF, ATRA, BDNF) on the expression of specific cholinergic genes in cellular models. Moreover, we find different sex-characteristic cytomorphology features including the length of axonal projections, numbers of synaptic connections, neurites length and branching patterns, which are important for developing specific *in vitro* models for targeted investigation of cholinergic molecular characteristics in men and women brains.

Advisor: Prof. Hermona Soreq