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Brainy Days in Jerusalem: The Future of Neuroscience – December 12-14th, 2022: Abstracts

Contents

Click the title to reach the specific abstract page!

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Accurate mechanistic modeling of zebrafish natural hunting behavior - a dynamical system approach

Yoav Rubinstein

Zebrafish movement repertoire is traditionally characterized by extracting dozens of body features of the body and clustering movements based on similarities in feature distributions. These clusters divide the continuous space of movements into a discrete set of 8 or 13 movement types depending on the clustering features. Such descriptive approaches lack a mechanism underlying movement generation, provide limited insights on movement neural control, and struggle to identify the natural primitives of movement - all are gateways to understand the principles of sequences of movements. In this work we propose a complete dynamical model with sparse controls that accurately generates zebrafish hunting movements. The model consists of two differential equations implementing a low-level internal oscillator with feedback on its amplitude, and a high-level control signal which represents the decision.

It reliably reconstructs the complete dynamics of 75% of movements. Our method dissociates the physical motor-related dynamics from the high-level decision-making process and thus predicts neural oscillation frequency as well as neural control strength and onset time. By reducing sequences of complex high dimensional movements into a sparse sequence of a two-dimensional control signal, it defines the primitives' space and forms a basis for understanding decision making and behavioral strategies.

Advisor: Dr. Lilach Avitan

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Action potentials in Inferior Olive neurons are triggered by localized intrinsic regenerative events.

Nora Vrieler

Other co-authors: O. Amsalem, Y. Lefler, I. Segev, M. Y. Uusisaar, Y. Yarom

Abstract:

The precise timing of Complex Spikes (CSs) in the cerebellar system is essential to its proper functioning; yet while it has long been known that CSs arise exclusively as action potentials (APs) in neurons of the Inferior Olive (IO), little is known about how IO neurons integrate information to generate APs. In this work, we explore this important question by studying APs and subthreshold activity recorded from IO neurons in vitro, and comparing APs and subthreshold depolarizing events that occur spontaneously to those elicited by activation of synaptic inputs to the recorded neurons. The results indicate that specific input pathways activate intrinsic regenerative currents in IO neurons, and that this mechanism is particularly powerful for activating APs in IO neurons. Finally, we use neuron models to explore possible arrangements of intrinsic regenerative currents that could lead to the experimentally observed phenomena, and find that they are most likely to be located in spine heads on or near the axon initial segment (AIS), where spine heads can indeed be seen to reside in anatomical data.

Advisors: Prof. Y. Yarom and Prof. M. Y. Uusisaari

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Active vision allows the perception of low-resolution images

Alexander Rivkind*, Or Ram*, Eldad Assa, Michael Kreiserman and Ehud Ahissar

Biological sensation is primarily active. Similarly to touch and whisking, visual perception in natural conditions, involves continuous sensor motion even during fixations between saccades. Perceptual mechanisms may either try to filter these eye movements out or, on the contrary, recruit them to obtain additional information about the stimulus. For example, when the gaze virtually "palpates" a perceived scene, fine spatial details are encoded by temporal delays. In theory, the visual system could use this temporal information to resolve tiny images for which spatial information is insufficient. We tested this hypothesis using artificial dynamical vision. For that we trained artificial recurrent neural networks that contain lateral connectivity in the early layers, to recognize images at low resolution using the temporally-coded information generated by sensor motion. We show that active vision, that involves sensor motion and recurrent processing, indeed allows the perception of low-resolution images, at a level that cannot be achieved with static stimulus or standard bottom up processing. Furthermore, echoing recent findings in human vision, we observed that the recognition performance of our system improved with the curvature of trajectory. Finally, we found that our network exhibits higher representational similarity to human fMRI data than the baseline feed forward networks.

Advisor: Prof. Ehud Ahissar

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An Investigation of the Number of Primary Dendrites In Human Purkinje Neurons

Karin Abu Haya

The layout and intricacy of the dendritic trees in neurons is related to the complexity of computations that can be performed by the nervous system. Purkinje neurons (PNs) are the principal neurons in the cerebellum, known to be highly intricate and forming a large number of synapses in the brain. In rodents, PNs are known to generally have a single primary dendrite arising from the neuron's cell body; however, intriguing results obtained in the Yarom lab indicated that for humans this may not be the case. In this work, we ask what is the percentage of human Purkinje neurons that have two primary dendrites arising from the soma. In order to quantify this we performed immunofluorescence experiments on fixed human brain tissue obtained from neurobiobanks, and counted PN somata and primary dendrites from images taken using a bright field microscope. The preliminary result from this investigation indicates that almost 90% of PNs in human have two (or more) primary dendrites. This study is of a major significance implying a qualitative difference in information processing in the cerebellar cortex (Cctx) distinguishing humans from other vertebrate species and can be the first step in understanding the expanded computational capabilities of the human cerebellar cortex.

Advisor: Prof. Yosef Yarom

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Auditory category learning of FM sweeps in mice

Or Cotev Yudco

Background and Methods: To make sense of highly complex environments, the brain uses categorization as a reduction mechanism. Category learning is the process of acquiring these rules of reduction, but the neural mechanisms underlying it are not well understood. Towards this goal, we studied how mice learn categories, and how are those represented in the cortex after learning. Using an automated learning platform, we trained mice to discriminate between two categories - rising frequency modulated (FM) sweeps and falling FM sweeps. We then challenged mice with a rich set of catch trials to decipher what they actually learned as the categorical rule. Next, we performed electrophysiological recording along different stations of the auditory cortex, in expert mice and naïve controls, using the multiarray silicon probe, Neuropixels.

Results: Mice learned to discriminate efficiently between rising and falling FM sweeps as well as to generalize in response to novel stimuli. Using catch trials we found that mice used the frequency content of the FM sweep as the rule for categorical boundary, rather than the slope of the sweep. Preliminary analyses of the electrophysiological data shows that single neuron shows better neuronal discrimination between FM sweeps as well as between pure tones, as compared to naive mice.

Conclusions: Mice use the frequency component of sounds to categorize FM sweeps. Category learning is accompanied by plastic changes in the response profile of single neurons in auditory cortex to sounds as simple as pure tones.

Advisor: Prof. Adi Mizrahi

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Auditory Perceptual Exercises in Adults Adapting to the Use of Hearing Aids

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Abstract

Background. Older adults with age-related hearing loss often use hearing aids (HAs) to compensate for their hearing loss. HAs have been shown to improve cortical and cognitive function (Karawani et al., 2018, 2022). However, certain challenges in speech perception, especially in noise still exist, and despite HA technology still people do not use HAs (McCormack & Fortnum, 2013). The current study presents an evaluation of a home-based auditory exercises program that can be used during the adaptation process for HA use.

Objectives. Our aim is to evaluate if the use of a home-based auditory training program and use of HAs can produce faster improvements in understanding and valuable subjective benefits in older adults with hearing loss through the first month of the adaptation to HAs. The home-based program was developed at a time when telemedicine became prominent in part due to the COVID-19 pandemic.

Methods. The study included 53 adults with age-related symmetrical sensorineural hearing loss. They were divided into three groups depending on their experience using HAs. Group 1: Experienced users (participants who used bilateral HAs). Group 2: New users (participants who were fit with bilateral HAs for the first time). Group 3: Non-users. These three groups underwent auditory training exercises for a period of three weeks. The auditory tasks included auditory detection, auditory discrimination, and auditory identification, as well as comprehension tasks presented in quiet and noisy listening conditions taking into consideration the model of Erber and Hirsh (1978). All participants completed self-assessment questionnaires before and after the auditory exercises program and underwent a cognitive test.

Results. Self-assessed improvements in hearing ability were observed across the HA users groups, with significant changes described by new users. Overall, speech perception in noise was poorer than in quiet. Speech perception accuracy was poorer in the non-users group compared to the users in all tasks. In sessions where stimuli were presented in quiet, similar performance was observed among new and experienced uses. New users performed significantly better than non-users in all speech in noise tasks; however, compared to the experienced users, performance differences depended on task difficulty.

Conclusions. The findings indicate that HA users, even new users, had better perceptual performance than their peers who did not receive hearing aids. A study to examine learning benefits of a longer training period with each protocol should be considered.

Implications and Contribution to the field statement. The current study promotes speech in noise perception by implementing different tasks in noise. This can supplement the diagnostic evaluation, especially when it is not completed because of time limitations of audiologists. The development of these home-based training programs has considerable potential to expand the type of interventions available and deliver them to older adults in their homes.

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Can winner-take-all mechanism underlie pop-out visual search?

Ori Hendler

Visual search is a goal-oriented activity we perform daily. It involves active scanning of the environment, with the goal of locating objects of interest in the background of irrelevant distractors. Here, we focus on pop-out visual search where the deviant object swiftly stands out and can be located with high fidelity. A widely accepted theory asserts that pop-out is computed by a winner-take-all competition between contextually modulated cells. However, past studies have shown that the ability of the winner-take-all mechanisms to accumulate information from large populations of neurons is limited; thus, raising the question whether winner-take-all can underlie pop-out visual search.

To address this question, we studied the pop-out task from the perspective of a readout mechanism and investigated the accuracy in which a winner-take-all mechanism can detect the deviant stimulus. We find that the performance of the winner-take-all deteriorates rapidly when the number of distractors is increased, while improving slowly with the number of neurons in each population. Moreover, applying the winner-take-all readout to electrophysiological data reveals that the inherent neuronal heterogeneity prevents the winner-take-all mechanism from achieving reasonable performance even in simple tasks with a small number of distractors. Finally, we show that a generalized population-code competitive readout can achieve the high performance expected from a pop-out mechanism. Nevertheless, our study indicates that individual bias (i.e. performance variability among different subjects) and deterioration of the performance with the number of distractors are expected to be found in the generalized population model too.

Advisors: Prof. Maoz Shamir and Prof. Ronen Segev

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Cerebellar circuit alteration in GRIN2D-DEE mouse model

Mor Yam, Jolan Nassir, Karen B. Avraham and Moran Rubinstein

The GRIN2D gene encodes for one of the subunits of the ionotropic glutamate NMDA receptor (NMDAR). The GRIN2D-V667I missense mutation is associated with developmental and epileptic encephalopathies (DEE), manifesting as early-onset epilepsy, motor deficits, developmental delay, and high mortality rate. Functional evaluation of this mutation in vitro demonstrated a gain-of-function effect. Yet patients' response to NMDAR antagonists is variable, indicating that the effect of this mutation on brain function may be more complex. Using cerebellum acute brain slices, of wild-type (WT) and Grin2d mutant mice, we studied how this genetic modification alters circuit activity.

Focusing on the activity of Purkinje cells, which are inhibitory neurons that have a critical role in motor learning and cognitive functions, we found that spontaneous firing frequencies in the mutant Grin2d mice were slightly lower, yet not significantly different, then those of WT mice. Next, patch-clamp recordings demonstrated reduced frequency and lower amplitude of spontaneous postsynaptic currents (sIPCs) in Grin2d mutant mice. These sIPCs were completely abolished in the presence of the GABAAR antagonist Picrotoxin, while Kynurenic acid, which blocks NMDAR and AMPAR had a much smaller effect, indicating that these are mainly inhibitory inputs. Interestingly, the addition of NMDA increased these sIPCs, with a tendency for a stronger effect in Grin2d mutant mice.

Together, these results indicate that although the mutation directly affects the NMDAR, it may also alter the activity of other ion channels, including GABAAR. To further examine the effect of the mutation on the cerebellar circuitry, we intend to perform electrophysiology recordings following stimulation to various targets in the cerebellum. Finding differences in the circuit activity in the mutant mice will promote our understanding of the neuronal mechanism of the disease and Grin2d in this circuit.

Advisor: Moran Rubinstein Ph.D

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Closing the neurofeedback loop - an overview on goal-dependent neurofeedback evaluation

Hadar Levi-Aharoni

In neurofeedback (NF) practice for clinical uses both therapists and patients would agree that a NF treatment was successful if a desired improvement in the clinical symptoms was achieved. This also applies to uses of NF for cognitive enhancement. Even researchers that criticize the lack of a mechanistic basis of NF treatments agree that such treatments achieve their goal in many cases and should be continued in some form.

In addition to the practical uses of NF, there is also a considerable amount of research on clinical NF, but some researchers and practitioners claim that this type of research is impossible for various reasons or debate over the right metrics. For example, successful NF treatments are individually adjusted for the patient by the NF therapist who tunes the parameters and selects the thresholds. Paradoxically however, in most studies that attempt to control this manual process by providing a uniform treatment for all patients - no advantage of NF treatment over sham NF is found. Such results even led researchers to suggest abandoning the basic NF hypothesis altogether (i.e.; the modulation of a specific neural activity) and propose focusing on other mechanisms such as placebo effects. Thus, while assessing the NF treatment from the point of view of the patient is straightforward, assessing it from the point of view of the researcher seems to be a much more complex task.

In clinical NF there are factors in play such as the goal, expectation and motivation of the patient etc. which add complexity to the evaluation of the NF training as a neural modulation method. Thus, there is merit in studying NF training effects on brain activity and behavior independently of the question of its clinical benefits.

Utilizing this simplifying approach, in NF for cognitive neuroscience researchers use NF for the goal of exploring the causal relations between neural representations and behavior. In this type of studies, a research paradigm can be asserted as successful only if NF control is acquired over the specific targeted neural representation and a causal effect on cognitive performance is shown. While in this approach some of the

complexities of clinical NF are eliminated, many other subject-specific factors may still play a central role such as the individual neural representation, learning rate and strategy, among others. In order to tackle all these remaining complexities, better characterization and evaluation procedures are needed. Researchers claim that "nearly 60 years of research have yielded surprisingly little evidence to support claims of regulatory brain-based mechanisms" [1]. However, a tool which allowed a tremendous leap in many other complex fields and is typically missing from the NF loop is machine learning and more broadly data science tools. These tools can allow a subject-specific characterization of neural representations which in turn allows a better specification of NF target and more precise post-NF evaluation. Importantly, utilizing these tools may also aid in removing some of the confounds and in explaining the contradictory results observed in the field.

[1] Robert T Thibault and Amir Raz. Neurofeedback: the power of psychosocial therapeutics. The lancet. Psychiatry, 3(11):e18, Nov 2016.

Advisor: Dr. Mor Nahum. (Abstract based on my PhD work done under the supervision of Prof. Naftali Tishby and Dr. Oren Shriki)

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Computational mechanisms underlying latent inverse value updating of unchosen actions

Ido Ben-Artzi

Current reinforcement learning studies suggest that individuals estimate the value of their choices based on observed feedback. Here, we ask whether individuals also update the value of their unchosen actions, even when the associated feedback remains unknown. Two hundred and three individuals completed a multi-armed bandit task, making choices to gain rewards. We found robust evidence suggesting inverse value updating for unchosen actions based on the chosen action's outcome. Computational modeling results suggested that this effect is mainly explained by an approach-avoid value updating mechanism whereby individuals integrate the outcome history for choosing an option with that of avoiding the alternative. Properties of the deliberation (i.e., duration/difficulty) did not moderate the latent value updating of unchosen actions, suggesting that memory traces generated during deliberation take a smaller role in this phenomenon than previously thought. We discuss the approach-avoid model as a possible manifestation of the dopaminergic D1 and D2 neural pathways.

Advisor: Dr. Nitzan Shahar

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Discrete communication mediates effective regularization in recurrent neural networks

Jan Philipp Bauer

Neuronal computation is mediated by spikes, yet it is unclear what the benefits of discrete spiking dynamics over continuous firing rates are. Many theoretical and computational studies treat single neurons as continuous units and their output as an effective firing rate. These works view spiking dynamics as a biophysical constraint, e.g., for energy efficiency. Conversely, other theories suggest that the exact timings of single spikes are meaningful. We propose a novel theory that shows the benefits of spiking dynamics on neural computation. In particular, we show that spiking neural dynamics can improve generalization, even when the information is encoded in the averaged firing rates and not in individual spikes.

Advisor: Jonathan Kadmon

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Does chronic pain predict cognitive decline and dementia in a population of older subjects? Results from the PAQUID study

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INTRODUCTION: Chronic pain (CP) was associated with impaired cognitive performance in several cross-sectional studies; however few longitudinal studies assessed the link. The present analysis was aimed at evaluating the prospective link between CP and the evolution of different cognitive functions and dementia risk in a population of elderly subjects. We hypothesize that the presence of CP could alter attention processes and memorization.

METHODS:

Population: from the PAQUID study, a cohort of 3777 community dwellers aged 65 and over; 768 subjects receiving a pain assessment were included.

Measures: CP was assessed with a self-rated questionnaire at 3-year follow-up.

A neuropsychological assessment was performed every 2-3 years between 3 and 15 years, assessing general cognition (MMSE), memory (Benton), attention and speed processing (Wechsler DSST, Zazzo's cancellation task) mental flexibility and language (Isaacs set test). Dementia was clinically assessed every 2-3 years for 24 years.

Statistical analyses: The link between 3-year CP and the evolution of cognitive performance over 15 years was assessed with multivariate mixed models controlled for age, gender, education, depression, psychotropic and analgesic drugs.

The association between CP and dementia risk over 24 years was assessed with Illness-Death models.

RESULTS: A significant relationship was observed between 3-year CP and poorer 15-year scores on MMSE ($p = 0.01$), Isaacs set test ($p = 0.03$), Benton ($p = 0.007$), and Wechsler DSST ($p = 0.0002$), whose CP influences slope of decline ($p = 0.003$). Conversely, no relationship was observed between DC and the risk of incident dementia ($p = 0.78$) or its time to onset ($p = 0.22$).

CONCLUSION:

CP is associated with lower overall cognitive performance, memory, attention and processing speed. The mechanisms are probably multiple: control of CP engaging frontal structures also involved in cognition, alteration of brain frontal areas involved both in endorphins production and attention and executive control, negative effects on cognition of neuromediators production induced by CP.

1. Rouch I, Edjolo A, Laurent B, Pongan E, Dartigues JF, Amieva H. Association between chronic pain and long-term cognitive decline in a population-based cohort of elderly participants. Pain. 2021 Feb 1;162(2):552-560. doi:10.1097/j.pain.0000000000002047. PMID: 32826758.

2. Rouch I, Edjolo A, Laurent B, Dartigues JF, Amieva H. Chronic pain and long- term dementia risk in older adults: Results from a 24-year longitudinal study. Int J Geriatr Psychiatry. 2022 May;37(5). doi: 10.1002/gps.5713. PMID: 35434855.

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Error origin detection and classification

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Abstract

Can we recognize error origins from brain activity? It is well established that an error spotted by a person evokes a brain response known as Error related potential (ErrP). ErrP is embedded in the ongoing Electroencephalography (EEG) signals. We hypothesize that errors of different types, accord a variety of situations, evoke different ErrP characteristic, determined by the nature of error. Here we examine the feasibility of error origin recognition and classification.

Current Brain Computer Interface (BCI) are prone to miss-classification with an error rate of about 30%. One of the solutions is to use ErrP as feedback signal for the BCI. Implementation of this approach in a step-wise motion task brought about significant decrease in error rate to below 10%. In order to farther improve this method, we propose to recognize error origin and follow with appropriate error correction suited to error nature.

With this goal in mind we compared ErrPs evoked by errors of different origin. In order to provide a valid comparison all errors were generated in the same experimental environment, with the same participants. Participants played a virtual 3D tennis-like game, against a computer player. The virtual game world was immersive, ecologically valid and provided a sense of physical forces via a haptic controller. The participant controlled a virtual tennis racket with a force feedback robotic haptic arm. The following error types occurred: (1) Outcome throwing errors - generated when the participant did not score a goal; (2) Outcome repelling internal user errors – generated when the participant missed a ball; (3) Execution external errors with congruent and incongruent visual and proprioceptive feedbacks – congruent errors generated by shift of the controlling hand, while incongruent are generated by shift of the virtual racket on a

screen only; and (4) External target errors – generated by unexpected inclination of the incoming ball.

These errors generated distinctive ErrPs. ErrP of each error type had its' own characteristic signal pattern, spectral response, cortex distribution and source localization. Consequently, it is possible to recognize the origin of error from analysis of its' ErrP. Theoretically, it is possible to build a smart error classifier based on the ErrP. This classifier can provide BCI with error tailored feedback, which in turn can be used for more efficient error correction. In addition, it can be used for diagnostic and rehabilitation purposes as a measure of patient capability to recognize the error origin. This can provide an index for the error management mechanism in the brain of a patient in conditions such as brain injury or stroke.

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Implementation of Iterative State Inference & Estimation of Uncertainty in Network Dynamics

John Schwarcz

The brain's ability to produce reliable behavior in a dynamic world is critical to survival. Humans and animals can respond quickly to subtle environmental changes, even when the underlying statistics are non-stationary. However, the neural mechanisms allowing this flexible computation are unknown. We developed a novel GO/NO-GO evidence accumulation task that requires simultaneous estimations of a hidden state and uncertainty. We trained mice and artificial neural networks (ANNs) to detect transitions between 'safe' and 'unsafe' states. In the safe state, a constant GO cue was played. In the unsafe state, a NO-GO cue was played with intermittent random misleading GO cues. The probability of a misleading GO cue in an unsafe state defines the noise level, which we control. The agent must strike a balance between speed and accuracy: acting prematurely may result in an error while waiting to remove uncertainty prolongs the trial and reduces the overall reward rate. Importantly, the optimal waiting time depends on the noise, which changes throughout the experiment. The challenge is that estimating the noise level requires evaluating the hidden state and vice versa.

Both mice and ANNs solved the task and presented similar qualitative behavior, adjusting their waiting times to the varying noise levels. We study the ANNs' neural dynamics and find a representation of noise estimation that matches that of an ideal Bayesian observer. We find that simple recurrent neural networks (RNNs) fail and do not adjust their behavior to the noise level as opposed to LSTM networks, which perform nearly optimally. Interestingly, modular RNNs with subcircuits trained to predict noise and state inference concurrently performed well. Our study points to the neural mechanisms that allow reliable state estimation in a changing environment. Furthermore, it suggests the benefits of a modular neural structure for flexible decision-making tasks.

Advisors: Jonathan Kadmon and Eran Lottem

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Increased Stability of Memory Retention through Multiple Synaptic Timescales

Georg Chechelnizki

Short term memory in the brain is theorized to often be implemented by continuous attractor networks, which represent stored variables in persistent neural activity. Since neurons are noisy, the variability in their activity degrades the memory, which can manifest as random diffusion. It was shown in (Lim and Goldman, 2013) that slow excitatory and fast inhibitory synaptic timescales can help decrease memory drift by providing negative derivative feedback to the system. Negative derivative feedback is known from control theory to increase robustness against various common perturbations. Building on this, it was shown that such a timescale difference also greatly reduces memory diffusion in a linear attractor network, as was shown in (Shaham and Burak, 2018). In this work we show for a far more general class of models that the degradation of memories by random diffusion can be mitigated by fast inhibition in conjunction with slow excitation. We derive a general expression for the diffusion coefficient of a stored variable in an attractor network of Poisson neurons with arbitrary connectivity and synaptic timescales as a generalization of a previous result for networks with a single synaptic timescale (Burak and Fiete, 2012). We then show that when we apply our theory to the negative derivative feedback scenario, it correctly predicts the increase of memory stability as a function of synaptic timescale difference in an exemplary ring model.

Advisor: Prof. Yoram Burak

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Involvement of Amygdala neurons in male predominance in Autism Spectrum Disorder

Noa Montefiore

Male predominance is one of the least understood characteristics of the Autism Spectrum Disorder (ASD). While more than a hundred genes are involved in ASD, recently it has had been suggested that only a few of them show sex differences in behavior. One of these genes is POGZ. Hence, in order to identify the molecular and physiological basis of male predominance we use Pogz+/- transgenic mice, a model for sex-specific effect in ASD (Suliman et al., 2019). Preliminary results from high resolution mapping and cFOS indicate the localization of the cells activated in social behavior differently in males and females in basolateral amygdala (BLA), a brain area which has been previously shown to be involved in sex difference social behavior tasks. In order to characterize the morphophysiological properties of the BLA neurons, which related to social behavior and are sexually dimorphic, we perform in vitro whole cell recordings targeted to cFOS-labeled cells of Pogz+/- mice. We aim to identify the populations of BLA neurons active in social behavior in Pogz+/- males and females and thus to suggest possible molecular and morphophysiological mechanisms of male predominance in ASD. The results of this study will shed a light on sex difference in ASD and thus advance the understanding of ASD.

Advisor: Yosef Yarom

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Longitudinal voltage imaging of Hippocampal neurons during virtual reality navigation

Yaniv Melamed, Rotem Kipper, Omer Cooper, Qixin Yang, Noa Garty, Shulamit Baror Sebban, and Yoav Adam

Hippocampal place cells are thought to comprise the building blocks for a cognitive map of space. Parallel intracellular recordings from the diversity of hippocampal cell types might help to shed light on the mechanism of place cell formation by providing full access to the subthreshold inputs as well as the spiking output of the different inhibitory and excitatory cells in the hippocampal microcircuitry. However, such recordings are hard to achieve using conventional electrode-based techniques. Here we present an experimental setup for in vivo voltage imaging combined with Optogenetic modulation in head-fixed mice navigating in virtual reality. To this end we expressed the genetically encoded voltage indicator Archon1, together with an optically orthogonal channelrhodopsin to gain all-optical control readout of the activity pyramidal cells and interneurons in the CA1 region of the hippocampus. Implanting a window above the expression site allows us to record voltage dynamics from head-fixed mice navigating in a virtual spatial task. Our optical setup, comprised of a patterned illumination microscope and a high-speed camera, allows video acquisition at 500-1000 frames per second. The resulting videos then go through a custom image processing pipeline optimized for voltage imaging data. We will present data of repeated imaging of pyramidal cells over weeks, demonstrating both spiking and subthreshold properties known from intracellular electrophysiological place cell recordings and their stability over time. In addition, we characterized the intracellular activity patterns of SST-positive interneurons during the spatial navigation task. Next, we will present preliminary data showing how these different cell types change their activity during Global Remapping, by "teleporting" the animals into a novel, unfamiliar virtual environment. Lastly, we demonstrate our ability to combine optogenetics in order to stimulate selected cells during navigation while recording others, which will allow us to further dissect the CA1 microcircuitry.

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Advisor: Prof. Yoav Adam

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Luxotonic amacrine cells constitute a neuronal hub that may contribute to luminance-dependent modulation of retinal function

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Background: The mammalian retina maintains high sensitivity over an extraordinary range of luminance levels, ranging from starlight to bright sunlight. This is achieved by switching between the rod and cone systems, and within each system, by employing light adaptation mechanisms that preserve a contrast-invariant response. While dopamine is known to modulate retinal network activity in proportion to luminance, the luminance-dependent signals and the circuits that transmit them to elicit light adaptation, remain elusive. We previously identified two luxotonic amacrine cells (LACs) selectively labeled in the Rbp4-Cre mouse: a polyaxonal wide-field amacrine cell (LAC1) and a novel, medium-field amacrine cell (LAC2). Considering that both LACs appear to stably encode ambient luminance, we hypothesized that LACs distribute signals across the retina and modulate the activity of inner retinal neurons in proportion to ambient luminance.

Aims: Selective manipulation of LACs will enable a pioneering investigation of their role in luminance-dependent modulation of retinal function. Moreover, a comprehensive exploration of the LAC system will allow us to put to the test our hypothesis that RACs distribute signals across the retina and modulate the activity of inner retinal neurons in proportion to ambient luminance.

Methods: As a first step toward testing this hypothesis, we used serial block face scanning electron microscopy to identify the pre- and postsynaptic partners of LACs. To identify bipolar cells (BCs) and amacrine cells (ACs) that synapse onto LACs, we surveyed the LACs dendrites for areas contacted by processes bearing ribbons (for BCs) and vesicle

aggregates (for ACs). Whereas, to identify BCs, ACs, and retinal ganglion cells (RGCs) that receive synaptic input from LACs, we screened for sites around presumptive pre- and postsynaptic specializations where LACs processes exhibit vesicle aggregations.

Results: The vast majority of presynaptic cells were BCs, particularly Type 6 BCs, that form en passant ribbon synapses with both LACs. The repertoire of cell types postsynaptic to LAC1 was rather limited and included ON BCs (Types 6 and 8) and several RGCs (eta-like, ON-OFF-direction selective, and M4 intrinsically photosensitive RGC – ipRGC). However, surprisingly, our reconstruction work revealed that LAC2 innervates at least 25 types of BCs, ACs, and RGCs. Postsynaptic cells included presumptive rod BCs and ON- and OFF-cone BCs with en passant synapses, AII and A17 ACs, various medium- and wide-field ACs (including LAC1 and LAC2, and ACs stratifying in the inner or outer inner plexiform layer, or both), dopaminergic ACs (DACs), nitric oxide synthase-1 ACs (NOS-1), vasoactive intestinal polypeptide-expressing ACs (VIP), vGluT3 ACs, JAM-B and OFF delta RGCs, and the M1 ipRGC. Thus, LAC1, and more so, LAC2, appear to be positioned as a neuronal hub that can regulate the sensitivity of diverse retinal neurons along the rod/cone pathways and along the ON/OFF pathways according to the ambient luminance.

Conclusion: Constructing the connectome of LAC1 and LAC2 is instrumental for understanding the functional roles of LACs, could enhance our understanding of luminance-dependent modulation of retinal function, and may provide a framework for the study of retinal light adaptation.

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Modelling state transitions of glial cells in Alzheimer's disease

Adi Ravid

Alzheimer's disease (AD) is a chronic and prevalent neurodegenerative disease characterized by progressive cognitive decline. Cognitive decline in AD is associated with accumulation of abnormal protein aggregates, specifically, Amyloid-Beta (Aβ), followed by synapse loss, neuronal damage and degeneration. In recent years, research focus has broadened beyond neuronal cells, uncovering changes in the brain's cellular environment. Using single nucleus RNA-sequencing (snRNA-seq) to unbiasedly profile cellular changes in a mouse model of AD, we found disease-associated cell profiles in all glial cell types, including oligodendrocytes, OPCs, astrocytes and microglia cells, suggesting an active role for non-neuronal cells in disease progression. We uncover signaling networks linking all the different glial cell types, yet the underlying cellular and molecular dynamics driving the state transitions in glial cells remains unknown. We thus use a spatial dynamic Bayesian model to simulate the dynamics of these state transitions of glial cells, from the common homeostatic state into the disease associated one, the effect of the cross-talk between the different glial cell types on these dynamics, as well as the drivers underlying the process. Our model simulates various scenarios of cellular crosstalk and molecular drivers that might explain AD progression and generates testable hypotheses for experimental validations.

Advisor: Dr. Naomi Habib

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Multi-cellular communities are perturbed in the aging human brain and Alzheimer's disease

Anael Cain

The role of different cell types and their interactions in Alzheimer's disease (AD) is an open question. Here we pursued it by assembling a high-resolution cellular map of the aging frontal cortex by single nucleus RNA-seq of 24 individuals with different clinicopathologic characteristics. Using our algorithm, CelMod, we used our cellular map to infer the neocortical cellular architecture of 638 individuals profiled by bulk RNA-seq, providing the sample size necessary for identifying statistically robust associations. We uncovered diverse cell populations associated with AD, including selective vulnerability of somatostatin expressing inhibitory neuronal subtype and specific oligodendroglial states. We further developed a computational scheme to find associations across cell types, which recovered a network of multicellular communities, each composed of coordinated subpopulations of neuronal, glial and endothelial cells. We found that two of these multi-cellular communities are altered in AD. Thus, our deconstruction of the aging neocortex provides a roadmap for evaluating the cellular microenvironments underlying AD and dementia.

Advisor: Dr. Naomi Habib

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Multi-cellular dynamics reconstructed across 424 aging human brains uncovers a distinct cascade leading to Alzheimer's disease

Gilad Green

Alzheimer's Disease (AD) is a progressive neurodegenerative disease for which recent studies have revealed AD-associated states across diverse cell types suggesting a system-level change in the cellular environment of the brain parenchyma. To distinguish cellular environment dynamics related to AD from aging-related effects, we analyzed single-nucleus RNA-seq from 465 prospectively collected aging cortical samples (DLPFC), spanning different clinicopathological characteristics of AD. We profiled 1.68 million nuclei and defined 96 cellular subsets across all cell types, forming a comprehensive cellular atlas of the aged DLPFC. On the individual cell type level, we uncovered cell subsets associated with AD-related traits. Of these, we prioritized two microglial and astrocyte populations associated with tau aggregates and cognitive decline, while the microglial cells were also strongly associated with amyloid-β plaques. Using a new algorithmic framework to investigate heterogeneity of cellular environments and to model their dynamics, we uncovered two distinct trajectories, both emerging from a cognitively healthy state and leading to different disease outcomes. One of these trajectories mapped to accelerated AD progression and showed a clear pattern of increased prevalences of Mic13 and Ast10. Clustering all cell subsets by their dynamics across both trajectories partitioned them into unique cellular communities, likely capturing coordinated cellular environments, including a rapid disease-associated, early-disease, slow-decline, and healthy cellular community. Applying a mediation model, we find that Mic13 partially mediates the effect of amyloid-β on tau (proportion mediated [p.m]=18%), and Ast10 partially mediates the effect of tau and Mic13 on cognitive decline (p.m=7.2% and p.m=12% respectively). Our unique cellular atlas of the aged human brain and novel approach for modeling cellular dynamics supports a system-level change in the cellular environment influencing disease outcomes, and highlight the distinct environments and dynamics underlying the rapid AD progression compared to a slower decline.

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Advisor: Dr. Naomi Habib

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Neural Correlates of Auditory Learning in Adolescence and Adulthood

Benne Praegel and Adi Mizrahi

Alexander Silberman Institute of Life Science, Edmond & Lily Safra Center for Brain Sciences,

Aims: Adolescence is known to be a period of uncertainty, exploration, and learning, yet there is little clarity about how even simple forms of learning change with development and are supported by neural circuits that undergo remodeling over the adolescent period. Here, we focused on mice and asked whether auditory learning in a go no-go task differs between adolescent and adult animals. Methods: To enable efficient learning of both adult and adolescent groups we trained freely behaving and head-fixed mice to perform a go no-go task of pure tones in a stable discrimination environment, and a volatile discrimination environment. After learning we recorded from expert head-fixed mice during discrimination performance. Extracellular recordings were carried out using ultra dense extracellular probes and targeted to deep layers of the auditory cortex. Results: While expert performance between adolescents and adults was similar, learning curves of adult mice were steeper. As compared to adolescents, we found that neurons in adult auditory cortex discriminate the go and the no-go stimuli better. This result was significant both at the single neuron level as well as at the population level. Conclusions: We identify clear differences between adolescent and adult auditory discrimination performance, which were accompanied by distinct neural correlates. We are currently evaluating the contribution of the orbitofrontal cortex on auditory discrimination and on cortical responses in the auditory cortex of adolescent compared to adult mice.

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Neural Correlates of Perceptual Learning Discrimination Task in the Auditory Cortex

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Background

Learning is a fundamental ability of the brain. Perceptual learning is an implicit form of learning, in which perceptual performance is improved. For example, repetitive experience with stimuli that are closely related to each other improves the animal's ability to distinguish between them. The underlying physiological correlates of perceptual learning remain unknown. Our aim was to study how exactly neurons increase the efficiency and precision by which they encode closely related sensory stimuli, using the auditory system as a model.

Results

We trained mice on an auditory Go-NoGo perceptual learning discrimination task while simultaneously imaging the auditory cortex with two-photon calcium imaging. Neuronal responses were monitored throughout learning while mice became experts on discriminating among distant and highly similar sounds. We image mice engaged in behavior and, separately, during passive listening. Single neuron responses to the sounds that mice trained on, were decreased in specific manner. This effect was reversible after the sound was no longer used in the task. Discrimination ability and inter-trial variability were higher during passive listening compared to engaged sessions. We also tested behavioral blocks during which mice switched between easy and hard discriminations. Switching revealed a significant increase in neurons' discriminability in the hard task. In addition, neural responses to the fixed stimulus were elevated in the hard task. Interestingly, the identity of neurons with the highest discrimination ability dynamically changed between sessions, particularly during hard discriminations.

Conclusion

Our work uncovers the auditory cortex as a highly dynamic landscape with encoding properties that are highly sensitive to behavior and perceptual demands.

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Neural dynamics and architecture of the heading direction network in a vertebrate brain

Hagar Lavian, Luigi Petrucco, You Wu, Vilim Stih, Fabian Svara, and Ruben Portugues

Animals can use different strategies to navigate. They may guide their movements by relying on external cues in their environment or by using an internal cognitive map of the space around them. An essential part of this representation are heading cells, neurons whose activity depends on the heading direction of the animal. Although those cells have been found in vertebrates, the full network was never observed and there is very little mechanistic understanding of how these cells acquire their response properties. In this study, we use volumetric functional imaging in larval zebrafish to observe a full network that encodes allocentric heading direction. This network consists of inhibitory neurons and is arranged in an anatomical circle in the anterior hindbrain. Single cell reconstructions of electron micrographs show that these neurons arborize the interpeduncular nucleus, where their connectivity pattern supports the implementation of a ring attractor network. The neurons we identify share features with neurons in the dorsal tegmentum nucleus of rodents and the fly central complex, showing that similar connectivity and mechanistic principles underlie the generation of cognitive maps of heading direction across the animal kingdom.

Advisor: Prof. Ruben Portugues

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Neural patterns differentiate traumatic from sad autobiographical memories in PTSD

Presenter: Ofer Perl

Ofer Perl[1,2,3], Or Duek[4,5], Kaustubh R. Kulkarni[1,2,3], Ben Kelmendi[4,5], Shelley Amen[4,5], Charles Gordon[4,5] , John H. Krystal[4,5], Ifat Levy[6,7], Ilan Harpaz-Rotem[4,5,7], Daniela Schiller[1,3]

For people with post-traumatic stress disorder (PTSD), recalling traumatic memories often displays as intrusions that differ profoundly from processing of 'regular' negative memories. These mnemonic features fueled theories speculating a qualitative divergence in cognitive state linked with traumatic memories. Yet to date, little empirical evidence supports this view. Here, we examined neural activity of PTSD patients who were listening to narratives depicting their own memories. An inter-subject representational similarity analysis of cross-subject semantic content and neural patterns revealed a differentiation in hippocampal representation by narrative type: Semantically similar sad autobiographical memories elicited similar neural representations across participants. By contrast, within the same individuals, semantically similar trauma memories were not represented similarly. Furthermore, we were able to decode memory type from hippocampal multivoxel patterns. Finally, individual symptom severity modulated semantic representation of the traumatic narratives in the posterior cingulate cortex. Taken together, these findings suggest that traumatic memories are a qualitatively divergent cognitive entity.

Advisor: Prof. Daniela Schiller

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New semi-quantitative contrasts can approximate R1 and R2 in clinical setting

Shachar Moskovich

Quantitative MRI (qMRI) allows to study the brain's microstructure. It has been recently proposed that with qMRI and relevant biophysical modeling, histological information about the human brain can be obtained in vivo. Nevertheless, in clinical settings, qMRI is rarely used. Clinical assessment using MRI is typically based only on weighted images, that are not suitable for microstructural analysis of brain tissue's biophysical properties. Similarly, many large open-source dataset of neurological disorders (e.g., PPMI, ADNI, UK-Biobank) have a large database of weighted images. Therefore, there is a great benefit in linking the widely available clinical MRI weighted data to known qMRI parameters.

In recent years, the ratio of T1 and T2 weighted images (T1w/T2w) has been suggested as a semi-quantitative indicator of tissue integrity and myelination and was linked to the pathology of Parkinson's disease. In this study, we propose using two additional weighted images ratios based on proton-density weighted image (PDw). We show that T1w/PDw and ln(T2w/PDw) can optimally represent the qMRI parameters R1 and R2 in the clinical setting. This was validated both on a controlled lipid phantom system and on a human dataset.

Advisor: Prof. Aviv Mezer

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Profiling the impact of Parkinson's disease on multifactorial aspects of attention

By: Ori Peleg

Background: Parkinson's disease (PD) is the second most common degenerative disorder of the nervous system, affecting about 2-3% of the population over the age of 65. One cognitive symptom of the disease, often undiagnosed, is attention dysfunction. The orienting of attention can be divided into two different networks: The endogenous – voluntarily network, initiated by internal goals, and the exogenous - involuntarily network, initiated reflexively. Studies suggest that the attentional dysfunction in PD may be due to unequal impairment in thus networks. However, the exact changes and contributions are yet unknown.

Objectives: (1) To characterize the differential effects of PD on the two attentional networks and (2) To examine the ability of attentional measurements differentiate between PD patients and Healthy controls (HCs).

Methods: Twenty PD patients and 20 HCs participated in the study that was designed to be conducted remotely on the patients' personal computers. Modified version of the Attention Network Test (ANT) has been used to study the attentional networks. Differences in ANT measures between and within groups were tested using Two-way ANOVAs. Multiple machine-learning feature selection and classification algorithms were applied to discriminate between PD and HCs.

Results: PD patients demonstrated worse performance in the attentional processes that require internal (endogenous) as opposed to external (exogenous) mechanisms ($F(1,37) = 4.75$, $p = 0.036$, $\eta^2 = 4.75$) compared to HCs. The Xgboost Machine learning demonstrated the highest discriminatory values between PD patients and HC with area under the curve (AUC) 0.93.

Conclusions: The endogenous – voluntarily attentional network is more susceptible to PD than the exogenous - involuntarily attentional network. Furthermore, applying machine-

learning to multiple ANT features reveals that different measures of attention discriminate between patients with PD and HC.

Advisors:

Prof. Daniel Levy, Baruch Ivcher School of Psychology, Reichman University.

Dr. Inbal Maidn and Prof. Anat Mirelman, Laboratory for Early Markers of Neurodegeneration (LEMON), Tel Aviv Sourasky Medical Center.

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Self-Body-Odor Repulsion in Sexually Assaulted Women

Romi Eli

Feelings of dirtiness and contamination, specifically elicited by a core feature of the self, are thought to play a significant role in sexually assaulted individuals. Victims frequently suffer from damaged self-image and are concerned that others will sense, smell, or see their contamination. They typically describe the feeling of being contaminated as permanent, becoming more aware of it when triggered by smelling their body odor (BO) (Brake et al., 2021) (Fairbrother & Rachman, 2004). BO can reveal a significant amount of information about an individual; a Previous study highlights the relevance of olfaction in bodily self-consciousness and shows its importance for modulating implicit aspects of embodiment.(Roel Lesur et al., n.d.). We set out to test the hypothesis that women who were sexually assaulted will recognize their own BO as repulsive or contaminated more than the control group.

To test this hypothesis, we will recruit twenty sexually assaulted women and 20 controls (who report that they did not experience a sexual assault). Each participant will wear a new (unwashed) T-shirt for two consecutive nights, which will be used as the odor stimuli in the experiment. Each woman will sniff and rate jars containing a t-shirt and rate the BO for perceived parameters such as intensity, disgust, dirtiness, and contamination. We will also measure galvanic skin response (GSR) for autonomic arousal while sniffing the shirts. We will utilize this data to study and assess the feelings of disgust and contamination elicited by one's body odor.

BO can reveal a significant amount of information about an individual; for example, several studies have examined the effect of human odor on kin recognition and mate choice (Porter, 1998) or the impact of familiarity on the recognition of nonrelatives by olfactory cues (Olsson et al., 2006). In another study, male and female sweat scents have been shown to influence aspects of embodiment (Roel Lesur et al., n.d.). Consequently, the above illustrates a possible reason why we frequently sniff BO of our own (Perl et al., 2020). Our research aims to shed light on how sexually assaulted women perceive their

self-BO and potentially suggest possible links between olfaction and bodily self-consciousness.

Advisor: Prof. Noam Sobel

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Slow maturation of olfactory circuits underlying innate odor preference

Elham Taha

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In mammals, odor information is transmitted from olfactory sensory neurons to mitral cells in the olfactory bulb. In turn, mitral cells transmit information to brain areas downstream, which are then read and executed as distinct behavioral output. Innate and learned behavioral responses are thought to be mediated by distinct neuronal circuits. Innate olfactory output is tunneled by mitral cells through the cortical amygdala (CoA). Learned olfactory output is tunneled by mitral cells through the anterior piriform cortex (aPC). How these two streams of information diverge remains unknown. In this project, our aim is to reveal how innate and learned olfactory circuits develop as the animals develops and ontogeny impacts behavior.

To that end, we performed anatomical and behavioral experiments. Anatomically, retrograde labelling of mitral cell through their axons in the aPC and CoA of adult and juvenile mice. In adults, we found a larger population of mitral cells projecting to the aPC as compared to the CoA. Importantly, the two populations are largely non-overlapping. In juvenile mice, the two circuits show distinct properties compared to adult mice. Behaviorally, Juvenile mice showed immature innate odor preference to both aversive and attractive odors. Taken together, these data indicate that odor processing of innate information matures late during postnatal development, because the distinction between innate and learned circuits is not yet established. Currently, we are using two photon calcium imaging to assess how mitral cells projecting to either aPC or CoA encode learned and innate odor information, respectively.

Advisor: Prof. Adi Mizrahi

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Stimulus-specific adaptation (SSA) in auditory cortex in awake mice under 2-photon microscopy

Moran Aharoni, Dina Moshitch, Israel Nelken

Stimulus-specific adaptation (SSA) is the response reduction to a common stimulus that does not, or only partially generalize, to other rare stimuli. SSA has been proposed to be a correlate of 'deviance detection', an important computational task of sensory systems. Human Electrophysiological correlates of deviance detection have been studied extensively using various brain potentials. The best known is mismatch negativity (MMN), which peaks ~150–200 ms after the deviant stimulus. SSA is similar, but not identical, to MMN. One difference between SSA in single cells and MMN is their time course. SSA 'rides' on the early cortical responses to sounds, whereas MMN occurs about 100 ms later.

Using fiber photometry of calcium signals in the mouse primary auditory cortex, we uncovered large and robust late response components which show deviance sensitivity at ~100-150 ms after stimulus onset. These signals are believed to reflect the average spiking activity of a local network.

To search for the single-neuron basis of those late population responses, we used two-photon microscopy to resolve the responses of multiple adjacent neurons. In the anesthetized mouse, we observed population activity that was robust and resembled the late responses components found using fiber photometry. However, single neurons hardly showed auditory responses independent of their surrounding neuropile. We therefore recorded in awake, head-fixed mice. In the awake mouse, we found more single neurons that responded to auditory stimuli independently of the surrounding neuropile. The late responses were however highly variable. We suggest that the reproducible late response components observed in the population activity reflect neuronal ensembles' activity whose membership varies between trials.

Advisor: Prof. Israel Nelken

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Syntactic and lexical mapping in awake craniotomy

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Intro

Typically, picture naming is the task widely used in awake craniotomies. Nevertheless, the more functions evaluated the more language areas will be maintained, leading to larger and safer resections. Although object naming may tap onto several language domains, including lexical-semantics, phonology, and in some cases morphology, it fails to assess language beyond the word level, such as syntactic structures.

The purpose of the current presentation is to demonstrate tools to identify syntactic areas in the brain during awake resection and to examine the possible added value of utilizing syntax paradigms in cortical and subcortical language mapping in awake craniotomy.

Method

Participants

47 patients aged > 16 years were scheduled for an awake craniotomy for a removal of de-novo tumor in proximity of regions involved in language, mean age 50.8 (SD = 16.0), harboring frontal (14), temporal (18, 10 insular) or parietal (14) lesions. All lesions but two are left sided, with left hemisphere language dominance. All patients were tested in their native language. Inclusion criteria included lesion due to a tumor and no language or cognitive deficits prior to the tumor. The lesion precise location is acquired pre, one day and three months post-operative via anatomical imaging scans.

Procedure

Data for each patient is collected and analyzed in two time-points: during the week before surgery and three months after the surgery. Each participant undergoes extensive language assessment in order to achieve a detailed evaluation of their syntax, including

Wh-movement, V-C movement, embedding and naming function, as well as reading, phonological buffer and lexical abilities.

According to the patient's preoperative status of syntax and naming, we assessed those functions intra-operatively, via cortical and sublexical language mapping during awake surgery. A demonstration will be presented in video-clips. To assess Wh-movement (with and without intervention) we used a subject- and object relative clause elicitation task, a relative clause comprehension task, and a sentence repetition task. If they were intact prior to surgery, these tasks were delivered to the patients while the surgeon performed a temporary Direct Electrical Stimulation (DES). In addition, three months following surgery we delivered to each patient a comprehensive postoperative language and syntax assessment, and then compared pre and post syntax functions:

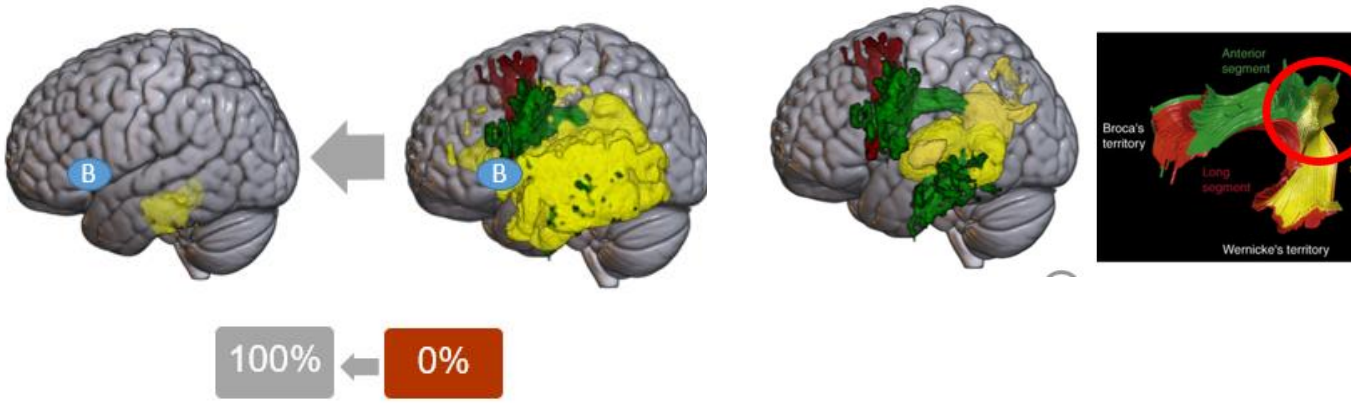
Results

With regard to syntax neuroanatomical substrates, we had 17 patients who showed a preoperative syntax impairment, with anterior lesions, covering large portions of the frontal or temporal lobes, and the frontal terminals of the aslant and the AF tracts. Most interestingly, in cases when postoperative MRI showed a full recovery of a preoperative damage to the Broca's area, following the surgery, those patients have also demonstrated a full recovery in their preoperative deficit in syntax. An important finding is that in contrast, other patients who, following surgery, still showed an impaired syntax post-surgery, had also a postop Broca's area damage (figure 1 a). In addition, impaired syntax also found in a second group of patients with tumors located near the AF bend. Unfortunately, those patients presented the same degree of syntax impairment on the postop examination (figure 1 b)

Discussion

Beside the clinical benefit of implementation of syntax functions mapping during awake language monitoring, DES contributed to our knowledge about the brain cortical and subcortical underpinnings of syntax processing.

Figure 1.



a Syntactic impairment following anterior lesion. A postoperative full syntax recovery following broca's area recovery

b Syntactic unrecoverable impairment following posterior lesion near the AF band

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The difference in relations between mAb1-42 and Abl kinase in excitatory and inhibitory synapses

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Abl kinase is a regulatory proteins, which acts differently depending on tissue type or cellular context. A wide spectrum of signals from outside and inside of the cell serve as triggers for Abl kinase activation: growth factors, DNA damage, cytokines, oxidative stress, and many others. Similarly, Abl response is multifaceted, triggering DNA repair or cell death, cell differentiation or proliferation, migration, or retraction. In the nervous system, Abl kinase is involved in neurulation, axon guidance, and synaptic transmission. Previous data from our laboratory showed that activation of Abl leads to a sharp reduction of spontaneous release in excitatory synapses, moreover, we found that suppression of spontaneous transmission induced by mA□42 (monomeric form of amyloid beta peptide) could be rescued by inhibitors of Abl kinase. Our recent data obtained from inhibitory synapses showed in opposite to the excitatory synapses Abl kinase's activation enhances spontaneous inhibitory synaptic transmission, suggesting that acute activation of Abl kinase is mediated by different signal transduction networks in excitatory and inhibitory synapses on the level of regulation of neurotransmitters release machinery. Interestingly, mA□42 reduced spontaneous inhibitory synaptic transmission, as in excitatory synapses. However, the most striking difference between the effect of mA□42-Abl kinase interplay in excitatory and inhibitory synapses was observed while Abl kinase inhibition failed to eliminate or even attenuate mA□42 induced reduction of inhibitory spontaneous release. Hence, similar suppression spontaneous synaptic transmission in excitatory and inhibitory synapses may be mediated by an independent signaling pathway, involving Abl kinase only in excitatory synapses.

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Advisor: Prof. Izhak Michaelevski

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The future, before and after: Bayesian and multivariate analyses reveal shared and unique neural mechanisms of imagining and remembering the same unique event

Inon Raz*, Avi Gamoran, Gal Nir-Cohen, Maayan Trzewik, Moti Salti, Talya Sadeh

Research shows that the brain regions that subserve our ability to remember the past are also involved in imagining the future. Given this similarity in brain activity, it remains unclear how brain activity distinguishes imagination from memory. In the current work, we scanned participants using fMRI before and after they performed a highly unique and elaborate activity wherein they went skydiving for the first time in their life. Multivariate pattern analysis, Bayesian inference, and a tightly-controlled experimental design were used to identify the neural activity that differentiates between memory and imagination of the same events. The results showed that large swaths of the Default Mode Network exhibited identical patterns of activity in recollection and imagination; several frontal areas were involved in imagination (but not in recollection), but no regions that were uniquely involved in recollection; the Precuneus was the only region that exhibited differential patterns of activity when thinking about the past vs. future. These findings join previous research concerning the crucial role of the Precuneus in our awareness of time, and suggest that recollection may be best seen as a sub-type of a broader process of mental simulation. As such, the results advance our understanding of the ways by which the critical distinction between the past and future is manifested in the brain.

Advisor: Dr. Michael Gilead,

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The Memory-Experience Gap: Effects of sleep-dependent consolidation and the quality of information remembered

Shira Darchi

Memory-Experience gap (MEG) is the gap between the average of emotions experienced during a given event and the retroactive, overall evaluation of the experience. The retroactive recollection is usually characterized by overestimation of the intensity of emotion experienced. Memory of an experienced event is affected by sleep-dependent consolidation, in which certain aspects of the event undergoes further processing and will be are better remembered, and others aspects, are forgotten. Surprisingly, there is a lack of consideration of essential memory processes such as sleep-dependent consolidation that might explain the MEG. The current study addressed this lacuna, by examining the effect of sleep-dependent consolidation on MEG. We used virtual reality (VR) as an innovative paradigm to create immersive, episodic experiences. Participants were randomly allocated into two groups: a sleep group and a wake group. In the first stage of the experiment, participants played several VR games and rated their emotions while playing. At the next stage, some participants slept, and the others listened to the podcast for an identical period of time. After this, all participants evaluated the emotions that they experienced during the first part. Mixed ANOVA analyses showed that the MEG is greater after sleep and that no MEG was formed without sleep. However, MEG was found only for positive emotions. The research hypotheses were partially confirmed. In general, the results of the present work indicate that the existence of MEG and its intensity are influenced by sleep-dependent consolidation processes for positive emotions.

Advisor: Dr. Talya Sadeh, Dr. Niv Reggev, Dr. Shachar Maidenbaum

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Topological schema of space in the orbitofrontal cortex

Raunak Basu, Ipek Bölükbaşı, and Hiroshi T. Ito

Animals in the wild often implement similar navigational strategies in a constantly changing environment. This ability is likely supported by the generalization of prior navigational experiences across similar contexts so that spatial memories can be reused in a given context. Previous research has identified place cells and grid cells in the hippocampus and the parahippocampal cortices that fire specifically when an animal visits a particular location. The spatial representations formed by these cells are sensitive to the difference in a behavioral context. For example, the change in a behaving room or maze shape elicits global remapping, whereby place cells and grid cells shift their spatial tuning, resulting in a new map orthogonal to the previous one. Such a phenomenon raises the question of how animals can maintain a consistent navigation strategy across environments where the underlying brain's map changes completely.

Here we report a novel spatial map in the orbitofrontal cortex (OFC) that preserves topological relationships of encoding positions in space. Rats were trained to alternate between two given locations on a linear track with ten equally spaced reward wells (Basu et al., 2021). While the rats performed this task, we observed that OFC neural ensembles exhibited distinct firing patterns depending on the animal's target location. Further analysis revealed that the difference in the ensemble firing patterns representing two locations is proportional to the distance between these locations in physical space. Hence, OFC neurons formed a spatial map preserving topological relationships of positions in a behaving arena. Next, to examine the similarity of the OFC map between contexts, we trained rats to perform the same task in the identical mazes located in two distinct rooms. In contrast to the hippocampal spatial map, the OFC neurons retained their location-specific activity across the two rooms, and at a neural ensemble level, the OFC map remained largely unchanged. Finally, to test if the OFC maps can be generalized across mazes with different geometry, we trained animals in two tracks with different shapes, either linear or circular, but with identical spacing between reward locations. We observed that the OFC neural ensembles formed a spatial map preserving topological

relationships of positions in both mazes, which could further be aligned using a rotation transformation. Taken together, the OFC forms a task-relevant schema of spatial positions by maintaining their topological relationships across environments, pointing to the OFC as a potentially crucial brain region for planning context-invariant navigational strategies.

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Visual perceptual stability is reflected in neuronal pattern similarities in visual cortex

Rotem Broday-Dvir

The amplitude of the visual neuronal response is commonly considered a critical factor of perceptual awareness. Yet, a major challenge to this notion comes from the dramatic phenomena of rapid visual adaptation, in which the response magnitude drops by more than 50% within 500ms of constant visual stimulation, while the perceptual experience remains stable. Here we examined the hypothesis that neuronal population activity patterns and their relational geometry, as defined by the dissimilarities between different stimuli-linked patterns, underlie sustained perception of visual stimuli, rather than the average response magnitude levels. 13 epileptic patients implanted with intra-cranial electrodes for clinical purposes viewed images of familiar faces and places, which were presented for 1.5 seconds, as part of a memory task. High-order visual cortex displayed strong, ignition-like responses, that rapidly declined despite the sustained stimulus presentation. On the other hand, the multi-contact activation patterns and their relational geometry- i.e. the correlation-based distances between different stimuli representations, were sustained for the entire stimuli duration. These results are compatible with the hypothesis that conscious perceptual content is associated with the neuronal pattern profiles and their similarity distances, rather than by the overall activation magnitude, in human visual cortex.

Advisor: Rafi Malach

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Voltage Imaging of pain signal initiation and propagation in nociceptors terminals

Efrat Sheinbach

Nociceptive terminals detect and transmit information regarding noxious stimuli, thus initiating pain sensation. Due to the small size of the terminals, direct electrophysiological studies could not be applied, and therefore little is known about terminal electrophysiology. We used genetically encoded voltage indicators (GEVIs) to directly monitor the voltage dynamics in the nociceptors terminals and thus characterize their electrical properties. To this end, we expressed the GEVI Archon1 in pain-sensitive neurons innervating the cornea. Using a custom patterned illumination microscope and a high-speed camera we succeeded to record electrical activity from single nociceptive terminals in anesthetized mice. Our results show that surprisingly, nociceptors are spontaneously active. The spontaneous spiking activity was observed both in cold-sensitive and hot-sensitive nociceptors. Local application of noxious stimuli evoked depolarization in the terminals and high-frequency spiking activity, which was mostly limited to the downstream axon, suggesting that the spike initiation zone is located between the terminal and the axon. To get insight into the mechanism of pathological pain, we will next test the electrical properties of the terminals during acute inflammation. Revealing the primary processes of pain encoding during health and disease will provide a novel understanding of the PNS spike initiation processes, and how it's differed from the well-studied processes in CNS neurons.

Advisors: Dr. Yoav Adam and Prof. Alex Binshtok

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What does it feel like to forget over time? An investigation of the effects of delay on objective and subjective measures of memory

Zohar Raz Groman

Recent years have seen a revived interest in the study of delay-dependent forgetting. The current study focuses on a fundamental question within the area of forgetting: how does delay affect subjective measures of memory and their relation with objective measures? This relation pertains to the intriguing question of whether humans are consciously aware of changes—or lack thereof— in the fidelity of their memory over time. We will present results showing that with time there is a substantial decrement in confidence, which does not correspond to the pattern of objective measures of forgetting. We maintain that the cues which drive subjective ratings of memory following delay do not reflect the fact that some aspects of memory show little or no forgetting. These cues may be based on individuals' biased theories of forgetting, and/or on the effort of retrieval which increases over time, even when the retrieved representation does not change.

Advisor: Dr. Talya Sadeh

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What is Social about Autism?

Meshi Djerassi

Scientific research on neuro-cognitive mechanisms of autism often focuses on circuits that support social functioning. However, autism is a heterogeneous developmental variation in multiple domains, including social communication, but also language, cognition, and sensory-motor control. This suggests that the underlying mechanisms of autism share a domain-general foundation that impacts all of these processes. We propose that autism is not a social deficit that results from an atypical "social brain". Instead, typical social development relies on learning. In social animals, infants depend on their caregivers for survival, which makes social information vitally salient. The infant must learn to socially interact in order to survive and develop, and the most prominent learning in early life is crafted by social interactions. Therefore, the most prominent outcome of a learning variation is atypical social development. To support the hypothesis that autism results from a variation in learning, we review evidence from neuroscience and developmental science, demonstrating that typical social development depends on domain-general processes that determine learning. We then review evidence showing that allostasis and learning are affected among individuals with autism, both neurally and behaviorally. We conclude by proposing a novel domain-general framework that emphasizes allostasis-driven learning as a key process underlying autism. Guided by allostasis, humans learn to become social, therefore, the atypical social profile seen in autism can reflect a domain-general variation in allostasis-driven learning.

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