Session A1

Chair: Orit Shefi

Neuromechanics and Neuroengineering

SUPER-RESOLVED INTERROGATION OF MOLECULES WITHIN THICK BRAIN TISSUES USING EXPANSION SEQUENCING

Shahar Alon, *Faculty of Engineering, Bar-Ilan University*

Molecular characterization of brain tissues using optical methods often present a problem of scale: on the one hand brain tissues are intrinsically three-dimensional (3D) structures, with thickness which can be 200 micrometers (fruit fly brain) or much larger; and on the other hand, nanoscale interrogation is needed to characterize molecules within neurites and synapses, which can be ~100 nanometers in diameter. Therefore, to characterize brain tissues, an imaging technology that allows super-resolution of thick tissues is required. Another challenge is the need for multiplexed interrogation of molecules: to characterize cell types and states inside brain tissues, and to detect deficiencies in neurological conditions, one needs to measure many different molecules in their original location (i.e., in situ) within the tissue. Currently, multiplexed imaging of molecules inside brain tissues is limited to thin sections (~10 micrometers), and almost impossible with super-resolution. Here we demonstrate multiplexed super-resolved characterization of thick brain tissues, including intact human brain organoids. We perform RNA sequencing within the expanded brain tissue, and use this technology, termed Expansion Sequencing, to measure nanoscale RNA distribution within neurites and synapses, and to detect molecular deficiencies in neurological disorders by comparing disease tissues to healthy controls.

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On spikes and sound in lipid membranes

Matan Mussel, *Department of Physics, University of Haifa*

The mechanism that underlies an action potential is widely considered to be electrical and is typically interpreted through a representation of the cell membrane as an equivalent electric circuit. The theory, however, relies on phenomenological equations that require many fit parameters. In addition, several experimental facts are neither readily explained nor predicted by electrical theory. For example, how thermodynamic variables--such as pH and extracellular viscosity--modify the pulse properties, and the co-propagation of mechanical and thermal variations with the electrical signal. After presenting these gaps, I will describe experimental and theoretical results of longitudinal pulses that propagate along lipid interfaces near the order-disorder phase transition. These pulses show remarkable similarities to action potentials, including their propagation velocity (~0.1—100 m/s), characteristic shape, a sigmoidal response to stimulation strength, annihilation upon collision, and an electrical aspect (~10-100 mV). Furthermore, the theory of sound can bridge some of the gaps of the electrical theory while using zero fit parameters. The talk will conclude by proposing that information encoded in the nonelectric aspects of the signal may be overlooked and discussing future experimental and theoretical challenges.

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The Mechanics of Action Potentials: Studying the Kinetics and the Cytoskeletal Origins

Adir Yarmus1, Dotan Kamber2, Rotem Shemesh Ben Yehuda2, Tamar Blumenfeld-Katzir2, Raya Sorkin4 and Uri Nevo2, *3*

1School of Physics and Astronomy,
2Department of Biomedical Engineering,
3Sagol School of Neuroscience,
4School of Chemistry, Tel Aviv University, Tel Aviv, Israel

Multiple evidence indicates that mechanical changes follow neuronal activity and affect neuronal function. However, the kinetics of these mechanical changes is not yet captured. In a recent study, we have shown ex-vivo that stimulation of the sciatic nerve led to a decrease in Microtubules' and Neurofilaments' density, the main contributors to the axon's elasticity. We developed a biophysical model of the interplay between neuronal activity and mechanical changes. We suggest that Myosin activity affects tension in active neurons within sub-second to seconds following firing. Indeed, accumulated evidence shows that Myosin activation occurs within milliseconds in synapses during neuronal activity. Additionally, Myosin activation is involved in cargo transport along the axon within seconds. Finally, Myosin contributes to axonal tension. Thus, we postulate that neuronal firing facilitates Myosin recruitment and increases axonal tension. In parallel, we aim to track and quantify the changes in cellular stiffness and tension associated with neuronal activity, in time scales of milliseconds to minutes. Additionally, we intend to elucidate the underlying cytoskeletal mechanisms associated with these changes. These are investigated experimentally using cultured neurons, with mechanical properties probed using Atomic Force Microscopy (AFM) before, during and following stimulation. Theoretical results and preliminary experimental results will be presented.

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Cell-type-specific detection of newly synthesized proteins in neurons in vivo to study the interplay between neuronal activity and translation during seizures

Or Shahar, *Galilee Research Institute, Tel Hai Academic College*

Newly synthesized proteins play key roles in neuronal activities such as memory consolidation. To better understand the interplay between neural activity and protein synthesis, we need to study mRNA translation within intact neurons. However, despite advances in methods to detect protein synthesis, measuring endogenous protein synthesis levels in vivo in an entire vertebrate brain is challenging. The complexity of the nervous system, comprising many cell types and long dendrites which are entangled in the respective tissue, makes it difficult to detect nascent proteins in neurons. Seizures constitute a condition with biological relevance in which neuronal activity is elevated. They can develop into the neurological disorder of Epilepsy, affecting over 70 million people worldwide. I will present a transgenic zebrafish line allowing for cell-type-specific labeling and imaging of nascent proteins across the entire nervous system. By replacing leucine 270 with glycine in the zebrafish Methionyl-tRNA-Synthetase (MetRS) binding pocket (MetRS-L270G), we enabled cell-type-specific incorporation of the non-canonical-amino-acid azidonorleucine (ANL) during protein synthesis. Since ANL contains an azide group, newly synthesized proteins can be labeled via 'click chemistry'. Specific expression of MetRS-L270G in neurons enables quantifying the intensity of neuronal protein synthesis. I will demonstrate the visualization of endogenous newly-synthesized-proteins across the nervous system, in specific brain regions and in dendrites of the translucent zebrafish larva, as well as changes in levels of nascent proteins following elevated neural activity and epileptic seizures.

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DEVELOPING A NOVEL BIOSENSOR FOR THE VISUALIZATION OF PTEN ACTIVITY

Tomer Kagan *Sackler School of Medicine, Yossi Levi Sackler School of Medicine, Sharbel Eid Sackler School of Medicine, Tal Laviv Sackler School of Medicine & Sagol School of Neuroscience*

Autism Spectrum Disorders (ASD) are closely associated with genes that regulate synaptic structure and function. One prominent example is the well-characterized tumor suppressor gene, Phosphatase and Tensin homolog (PTEN). Germline mutations in PTEN are frequent in those diagnosed with ASD, macrocephaly and multiple types of cancer grouped as PTEN Hamartoma Tumor Syndrome (PHTS). However, it still remains unknown how PTEN signaling dynamics modulate ongoing neuronal function in the brain. To monitor the activity state of PTEN in living cells, we have developed a novel FRET based PTEN sensor, optimized for two-photon fluorescent-lifetime imaging (2pFLIM). Our biosensor is composed of a modified PTEN flanked by a FRET donor and acceptor, allowing dynamic monitoring of changes in PTEN conformation as a proxy of its activation. We use CRISPR/Cas9 gene disruption, multiple color-shifted variants and live-imaging of PTEN activity, to unravel subcellular changes in PTEN activity differentially affecting somatic and synaptic PTEN in multiple cell types using in-vivo 2pFLIM. Overall, our experimental strategy enables monitoring PTEN activity with unparalleled spatial and temporal resolution to determine how PTEN dynamics in-vivo maintain neuronal development and plasticity. These insights will be fundamental to unravel the core mechanisms leading to neuronal dysfunction in ASD, PHTS and macrocephaly.

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VISUALIZING NEURONAL CYTOSKELETON IN SUPER RESOLUTION TO ANALYZE SELF-REPAIR MECHANISMS

Oz Mualem, *Faculty of Engineering Nanotechnology Institute and Gonda Multidisciplinary Brain Research Center Bar-Ilan University Ramat Gan Israel*
Zehavit Shapira, Faculty of Engineering Nanotechnology Institute and Gonda Multidisciplinary Brain Research Center Bar-Ilan University Ramat Gan Israel
Allegra Coppini, Department of Biology University of Pisa Pisa Italy Alessandro, Falconier, Department of Biology University of Pisa Pisa, Italy Syeda Rubaiya, Nasrin, Department of Physics Graduate School of Science Kyoto University Kyoto Japan Gadiel, Saper, Department of Biomedical Engineering Columbia University New York USA Henry, Hess, Department of Biomedical Engineering Columbia University New York USA Akira, Kakugo, Department of Physics Graduate School of Science Kyoto University Kyoto Japan Vittoria, Raffa, Department of Biology University of Pisa Pisa Italy Orit, Shefi, Faculty of Engineering Nanotechnology Institute and Gonda Multidisciplinary Brain Research Center Bar-Ilan University Ramat Gan Israel

Axons are vital extensions of neurons that vary in length and transmit electrical signals away from their cell body. Although considered delicate structures, axons have the noteworthy ability to withstand millions of cycles of bending and stretching throughout a person's lifetime. This remarkable resilience of axons is attributed to the presence of several biological self-repair mechanisms. Nevertheless, these mechanisms remain insufficiently characterized or researched. This is partly due to the dense and bundled arrangement of the neuron’s cytoskeleton, which hinders the resolution of its detailed structure. To address this challenge, we employ a cutting-edge super-resolution technique, which allow us to surpass the diffraction limit and examine the neuron’s cytoskeleton at a nanometric scale. Our research seeks to uncover vital insights into the neuron's intricate structure and explore their potential self-repair mechanisms it may possess. In all, our work can enhance the comprehension of neuronal resilience and pave the way for potential biomedical applications in research and technology.

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Session A2

Chair: Rita Schmidt, Edna Furman-Haran

Functional differences between individuals - what can we learn from long- and short-term signal variations in the human brain

Substantia nigra and putamen asymmetries explain motor dysfunction in Parkinson's disease

Elior Drori and Aviv Mezer, *The Hebrew University of Jerusalem*

Parkinson's disease (PD) is associated with degeneration of the nigrostriatal dopamine system, involving the substantia nigra (SN) and the putamen. We recently showed that in vivo gradients in the putamen are related to early-stage PD symptoms. However, it is not clear whether putamen and SN degenerations reflect common, rather than distinct, pathologies. Here we tested whether asymmetries in the SN and putamen are related to PD-related motor dysfunction across MRI visits. Our findings suggest different sources may underlie the signal in the putamen and the SN and show that a multi-ROI analysis adds substantial value for explaining PD motor behavior. Results We found that normalizing T1w/T2w images (see methods) reduces the image variability within- and between-subjects. We then used 356 normalized images of N=146 PD patients and 119 normalized images of N=64 Healthy controls (HC). We found that contralateral symptoms are associated with higher SN intensity and lower putamen intensity. These results suggest that while asymmetry in the putamen may be driven by tissue degeneration, SN asymmetry may be driven by iron content. We found that putamen and SN asymmetries together better explain the patients' motor behavior, suggesting pathologies that are not entirely shared between the regions.

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Functional connectivity gradients and their association with thought-patterns in Schizophrenia patients with negative symptoms

Tal Geffen (*Charité – Universitätsmedizin Berlin, Department of psychiatry and Psychotherapy, Berlin, Germany*)
Samyogita Hardikar (.Max Planck Institute for Human Cognitive and Brain Sciences, Department of Neurology, Leipzig, Germany/ Queen's University, Department of Psychology, Kingston, ON, Canada), Jonathan Smallwood (Queen's University, Department of Psychology, Kingston, ON, Canada), Mariia Kaliuzhna (University of Geneva, Clinical and Experimental Psychopathology Laboratory, Faculty of Medicine, Geneva, Switzerland), Fabien Carruzzo (University of Geneva, Clinical and Experimental Psychopathology Laboratory, Faculty of Medicine, Geneva, Switzerland), Teresa Katthagen (Charité – Universitätsmedizin Berlin, Department of psychiatry and Psychotherapy, Berlin, Germany), Priska Herger (Independent Researcher), Stephan Kaiser (Geneva University Hospital, Adult psychiatry division, Department of Psychiatry, Geneva, Switzerland), Florian Schlagenhauf (Charité – Universitätsmedizin Berlin, Department of psychiatry and Psychotherapy, Berlin, Germany/ Bernstein Center for Computational Neuroscience, Berlin, Germany)

Background: We examined thought-patterns and connectivity gradients [1] in schizophrenia-patients (SZP) and compared them to healthy-controls (HC). Previous research has explored these patterns in HC.

Method: 77 SZP and 66 HC underwent a 9.8-minute resting-state-fMRI scan and provided thoughts during the scan using Multi-Dimensional-Experience-Sampling [2]. Thought-patterns components were extracted using Principal-component-Analysis (PCA) and compared between groups. Cortical connectivity gradients were created using PCA and a group-comparison was made on parcel and network levels. A General-Linear-Model was computed based on group and Thought-patterns, predicting connectivity values.

Results: show that SZP has lower Abstract-Spontaneous thought-pattern values and higher Intrusive-Negative thought-pattern values than controls. Gradient analyses reveal that SZP exhibits greater dissociation between attentional-related networks to the Default-Mode-Network (DMN) and more similarity to sensorial networks. The second gradient, representing a transition between two sensorial networks, was significantly shorter among SZP, reflecting more similarity of the different network's connectivity pattern in SZ. This replicates previous findings on the subject. Three parcels differed significantly between the groups, replicating some of the network-level findings. Furthermore, the Gradient-location of a parcel from the G2_Somatomotor network could be predicted based on the group and the Abstract-Spontaneous thought-pattern.

Conclusion: The Multi-Dimensional-Experience-Sampling can effectively assess thought-patterns and distinguish between the groups. The findings suggest that SZP exhibits greater similarity between attention-related networks to sensorial networks, as well as more dissociation from the DMN. Additionally, thought patterns can serve as significant predictors for brain connectivity.

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Increasing sensitivity in fMRI to study individual differences – advantages of high field human MRI

Rita Schmidt, *Department of Brain Sciences, Weizmann Institute of Science*

The importance of capturing individual brain fingerprints (both functional and microstructural) has become well recognized in recent years. This shift to individual analysis approaches became feasible with the new advances in MRI – e.g., higher field strengths and faster acquisition techniques – which improve contrast-to-noise and signal-to-noise ratios (CNR, SNR). We utilized a new 7T MRI scanner and an optimized multi-echo approach to increase both the CNR and the achievable temporal resolution in a motor task experiment comprised of finger tapping patterns of varying complexity levels. Our target, in this case, is the basal ganglia which is associated with preparation, planning, and learning processes, and is especially challenging for imaging with MRI due to its high iron content. In addition, we have designed a task-based experiment that combines auditory and motor stimuli. In standard auditory experiments an external auditory stimulus is added on top of the acoustic noise of the MRI scans. Here, we implemented a new approach employing the acoustics of the acquisition itself to generate the auditory stimuli. The new approach offers stimuli with high temporal accuracy which are well-synchronized with the scan. The above methods improve the measured sensitivity and can therefore better characterize individual differences.

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Relating Activity and Connectivity in the Learning Brain

Ido Tavor, *Faculty of Medicine and Sagol School of Neuroscience, Tel Aviv University*

Brain activity while performing tasks is closely related to connectivity. Using machine learning, we show that connectivity patterns obtained from resting-state scans predict individual differences in brain activation in healthy individuals and psychiatric patients. We further demonstrate that models can be generalized across datasets, sites, MRI vendors, and age groups, suggesting that it may be possible to train a model using publicly available datasets and test on smaller, boutique' datasets. Next, we show that task-activation maps predicted from functional connectivity can be used to predict individual traits. Therefore, predicted task-activation may serve as a novel representation of connectivity that may enhance brain-behavior associations. Finally, activity and connectivity are not fixed but undergo modifications following learning. In a series of studies, we examined the relations between task-activation and functional connectivity, and the predictability of the former from the latter, in the learning brain. Participants underwent scans before and after either piano training or a sign-language course. We show learning-induced modifications in connectivity and activity and their associations with one another and with performance. We conclude that connectivity and task-induced activity may share a common neural representation, and that connectivity may play a mechanistic role in brain activity and behavior.

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Living the inverted "U": Connecting the ups and downs from fetus to grave in movement and cognition

Gerry Leisman, *Movement & Cognition Laboratory, Department of Physical Therapy, University of Haifa and Resonance Therapeutics Laboratory, University of the Medical Sciences, Havana, Cuba*

The process of learning commences relatively early in fetal development and progresses until our last moments. Cognitive growth is not simply linear, but rather an inverted "U" with much that connects the early development of associational circuits and their decrement in aging. We overview the nature of movement and cognition through the lens of human development emphasizing processes that stimulate multiple neural connections that promote memory. For optimal learning, the brain requires conditions under which it can promote and support neuroplasticity and neurogenesis. Learning is the most effective involves recruiting multiple regions of the brain for learning tasks. These regions are associated with functions such as memory, sensation, volitional control, and higher levels of cognitive functioning. More complex thought processes are more beneficial for learning because they involve a greater number of neural connections and more neurological crosstalk. Active learning takes advantage of this crosstalk, stimulating a variety of areas of the brain and promoting memory. We will discuss the nature of this progression during one's lifetime, connecting developmental with the decremental processes in the context of learning un employing small v. large world networks in cognitive tasks associated with age from fetus to end-of-life.

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Dissociating Distinct Cortical Networks Associated with Subregions of the Human Medial Temporal Lobe

Daniel Reznik - *Department of Psychology, Max Planck Institute for Human Cognitive and Brain Sciences, Leipzig, Germany*
Robert Trampel - Department of Neurophysics, Max Planck Institute for Human Cognitive and Brain Sciences, Leipzig, Germany Nikolaus Weiskopf - Department of Neurophysics, Max Planck Institute for Human Cognitive and Brain Sciences, Leipzig, Germany; Felix Bloch Institute for Solid State Physics, Faculty of Physics and Earth Sciences, Leipzig University, Leipzig, Germany Menno P Witter - Kavli Institute for Systems Neuroscience, The Egil and Pauline Braathen and Fred Kavli Centre for Cortical Microcircuits, Jebsen Centre for Alzheimer's Disease, NTNU Norwegian University of Science and Technology, Trondheim, Norway Christian F Doeller - Department of Psychology, Max Planck Institute for Human Cognitive and Brain Sciences, Leipzig, Germany; Kavli Institute for Systems Neuroscience, The Egil and Pauline Braathen and Fred Kavli Centre for Cortical Microcircuits, Jebsen Centre for Alzheimer's Disease, NTNU Norwegian University of Science and Technology, Trondheim, Norway; Wilhelm Wundt Institute of Psychology, Leipzig University, Leipzig, Germany; Department of Psychology, Technische Universität Dresden, Dresden, Germany

Tract-tracing studies in primates indicate that different subregions of the medial temporal lobe (MTL) relate to multiple brain regions. However, no clear framework defining the distributed anatomy associated with the human MTL exists. This gap in knowledge originates in notoriously low MRI data quality in the anterior human MTL and in group-level blurring of idiosyncratic anatomy between adjacent brain regions, such as entorhinal and perirhinal cortices, and parahippocampal areas TH/TF. Using MRI, we intensively scanned four human individuals and collected whole-brain data with unprecedented MTL signal quality. Following detailed exploration of cortical networks associated with MTL subregions within everyone, we discovered three biologically meaningful networks associated with the entorhinal cortex, perirhinal cortex and parahippocampal area TH, separable from area TF. Our findings define the anatomical constraints within which human mnemonic functions must operate and are insightful for examining the evolutionary trajectory of the MTL connectivity across species.

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Session A3

Chair: Ilana Gozes, Haitham Amal

Psychiatric disorders: from molecular mechanisms to drug targets

WHICH PROCESSES CONTROL NOVEL CHOLINERGIC-TARGETING MICRORNAS INTEGRATED INTO THE PRIMATE GENOME?

Hermona Soreq, *The Hebrew University of Jerusalem*

Objectives: Numerous microRNAs (miRs) are primate-specific, but how their expression is regulated is elusive. We studied how hsa-miR-608, located in the 3rd intron of the primate Semaphorin 4G gene targets the pro-inflammatory cytokine interleukin-6 (IL6) and the acetylcholine hydrolyzing enzyme acetylcholinesterase (AChE), affecting the cholinergic blockade of inflammation.

Methods: We established transgenic mice expressing miR-608 flanked by 250 nucleotides-long regions from the 3rd intron of the mouse Sema4g gene and employed cell transfection tests and pulldown-mass spectrometry profiling to challenge the consequences.

Results: The 'humanized' mice expressed miR-608 in several tissues, indicating regulation of miR-608 expression by its surrounding genomic sequences. Transfecting miR-608 flanked by its human genome regions identified an active promoter 5' to pre-miR-608 which elevated miR-608 levels by 100-fold. Pulldown-mass spectrometry revealed binding of ribosomal protein L24 (RPL24) with the tested 150 nucleotides-long sequence, which inhibited miR-608 expression. RPL24 interacted with the DDX5 component of the large ribosomal complex, and its depletion altered the levels of 22 other miRs.

Conclusions: Implicating RPL24 in pan-evolutionary supervision of miRs biogenesis, primate RPL24 binds to a 5' sequence of pri-miRs, reducing their levels, and interacts with the DDX5 component of the microprocessor, mimicking its miR processing role in Arabidopsis thaliana.

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ADNP/NAP (DAVUNETIDE) PROTECTION IN BRAIN DISEASES IS SEX-DEPENDENT

Ilana Gozes, *Tel Aviv University*

Objective: We aim to decipher the molecular mechanism underlying brain disease sexual dichotomy toward personalized medicine.

Methods: We focus on activity-dependent neuroprotective protein (ADNP), essential for brain formation and when mutated in humans drives tauopathy/intellectual disability, cognitive impairment, social and motor deficits. We analyze animal models and clinical data.

Results: We discovered a short neuroprotective motif in ADNP, NAP (davunetide), providing neuroprotection through microtubule/cytoskeletal fortification, in two mouse models, Adnp+/- and genome edited to include heterozygous Adnp mutation leading to early-onset Alzheimer's disease (AD) -like tauopathy, accentuated in male compared to female mice and corrected by NAP treatment. ADNP regulates sex-steroid, affecting hundreds of genes, associated with chromatin remodeling and protects against tauopathy. Axonal transport was sex-dependently controlled in the Adnp+/- mice, while sex-differential regulation of dendritic spine formation was most obvious in the genome edited ADNP heterozygous mutated mice, corrected by NAP. Clinically, we revealed sex differences indicating davunetide mediated
efficacy in women suffering from the pure tauopathy, progressive supranuclear palsy (PSP).

Conclusions: Understanding sexual dichotomy is essential for rational drug development.
Gozes I, Shapira G, Lobyntseva A, Shomron N.Transl Psychiatry.

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THE ROLE OF MITOCHONDRIAL DYSFUNCTION IN THE EARLY BRAIN DEVELOPMENT OF ANGELMAN SYNDROME

Lilach Simchi - University of Haifa, Pooja Kri Gupta - University of Haifa, Yonatan Feuermann - University of Haifa, Hanoch Kaphzan - *University of Haifa*

Angelman syndrome (AS) is a genetic autism spectrum disorder (ASD) characterized by a developmental delay, lack of speech, motor dysfunction, epilepsy, autistic features, and intellectual disability. AS is caused by the loss of function of the UBE3A gene. UBE3A is known to be an E3-ligase, but its cellular roles are not completely clear. Recently, we showed that the lack of UBE3A function is associated with aberrant mitochondrial functioning and elevated mitochondrial reactive oxygen species (mROS) levels. Moreover, we showed that this multifaceted mitochondrial dysfunction is evident during early brain development affecting neural precursor cells (NPCs). NPCs lacking UBE3A exhibit elevated mitochondrial membrane potential (ΔΨm), lower levels of endogenous reduced glutathione, excessive mROS levels, and increased apoptosis. Furthermore, we demonstrated that glutathione replenishment did not recover the elevated ΔΨm but normalized the excessive mROS levels and rescued the enhanced apoptosis. Taken together, we conclude that there is a point of no return in the early stages of brain development of AS, but early intervention can rescue some of the aberrant cellular anomalies. Given that many ASDs share similar features with AS and entail enhanced oxidative stress, we suggest that mitigating mitochondrial dysfunction during embryonic development could alleviate ASD.

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A Crosstalk between nitric oxide and mTOR signaling pathway in autism spectrum disorder (ASD)

Shashank K. Ojha, *The Hebrew University of Jerusalem*
Manish K. Tripathi, The Hebrew University of Jerusalem
Maryam Kartawy, The Hebrew University of Jerusalem
Haitham Amal, The Hebrew University of Jerusalem

Objectives: The objectives of this study were to investigate the role of nitric oxide (NO) and the mTOR signalling pathway in the pathology of autism spectrum disorder (ASD). We examined the effects of excessive NO levels in mice carrying Shank3 and Cntnap2 mutations on nitrosative stress, S-nitrosylation (SNO) of synaptic proteins and on mTOR signaling. Additionally, the study aimed to evaluate the effects of pharmacological inhibition of NO using HU-53.

Methods: The biochemical experiments were conducted in vivo as well as in vitro to test for nitrosative stress and SNO of synaptic proteins. The effects of HU-53, a pharmacological inhibitor of NO, were also examined.

Results: The study showed that mutant mice exhibited decreased levels of synaptic proteins, accompanied by increased phosphorylation of mTOR and RPS6. The expression of NR1 and GAD1 were also altered. Treatment with HU-53 reversed these changes, protecting against excessive NO production. These findings indicated that excessive NO production induced by Shank3 and Cntnap2 mutations resulted in abnormal mTOR signaling and disrupted synaptic neurotransmission.

Conclusions: These findings suggest that targeting NO production could be a potential therapeutic approach for ASD, with implications for restoring normal synaptic function and alleviating symptoms associated with the disorder.

Session A4

Chair: Chaya Kalcheim

Sensory systems: from development to function

REGULATION OF DYNAMIC CELL FATE TRANSITIONS DURING SPINAL CORD DEVELOPMENT

Chaya Kalcheim, *Hebrew University*, IMRIC and ELSC
Dina Rekler, Hebrew University, IMRIC and ELSC
Shai Ofek, Hebrew University, IMRIC and ELSC
Susanna Ventriglia, Hebrew University, IMRIC and ELSC
Sarah Kagan, Hebrew University, IMRIC and ELSC
Gilgi Friedlander, Weizmann institute of Sciences, Bioinformatics Unit

The separation between central and peripheral branches of the nervous system (CNS and PNS), takes place in the dorsal neural tube (NT). This domain sequentially generates neural crest (NC), progenitors of the PNS, followed by the roof plate (RP) of the CNS, crucial for development and patterning of adjacent interneurons. Subsequently, RP cells stretch to generate the dorsal midline radial glia (RG), a a source of dorsal ependyma. The mechanisms underlying the end of NC production and consecutive formation of the definitive RP and RG, are largely unknown. We report that dNT-derived retinoic acid (RA) is responsible for the completion of NC production and emigration, acting through suppression of BMP and Wnt signaling. Moreover, RA acts upstream of Notch to generate the RP-interneuron boundary. Inhibition of RA activity prolonged the lifetime of the NC while generating a bipotent peripheral glia-melanocyte progenitor. Furthermore, in absence of RA input, single cells co-expressed NC, RP and interneuron traits. This implies that the spatial and temporal segregation of these lineages relies on a network involving RA and BMP/Wnt/Notch. Together, we expect to achieve a novel understanding of dorsal spinal cord ontogeny, and of possible mechanisms conducive to abnormal development.

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MOLECULAR AND STRUCTURAL PLASTICITY OF NOCICEPTIVE PERIPHERAL TERMINALS UNDERLYING PATHOLOGICAL PAIN

Alexander Binshtok, *The Hebrew University of Jerusalem*

Nociceptive free nerve endings are specialized for the detection of harmful stimuli. Because these tiny structures are the most physiologically relevant site of pain detection, understanding the molecular network underlying nociceptive terminal functionality and its modulation in different pain states is imperative for understanding the mechanisms of normal and pathological pain. Recently, we have developed approaches to optically record the activity of single nociceptive terminals in vivo. Using the genetically encoded calcium and voltage indicators expressed by nociceptive terminals and axons, we monitor the generation of signals induced by noxious stimuli at the terminal tip and follow its propagation along a single nociceptive fiber. We dissected the molecular network underlying the signal generation and propagation along the single terminal tip and fiber and explored the changes in this network underlying inflammatory pain. We analyzed how signals from single terminals are integrated along the terminal tree and predicted how the alteration of terminal tree structure affects the input-output properties of the nociceptive neurons. We demonstrated that inflammation induces changes in the structure of a terminal tree by activating the mTORC2 complex and that these changes are sufficient to produce pathological pain.

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Detection and Neural Encoding of Whisker- generated Sounds in Mice

Michael Sokoletsky (Weizmann), Yonatan Katz (Weizmann), Ilan Lampl (*Weizmann*)

To uncover the neural correlates of stimulus perception, experimenters commonly use tasks in which subjects are repeatedly presented with a weak stimulus and instructed to report, via movement, if they perceived the stimulus. The difference in neural activity between reported stimulus (hit) and unreported stimulus (miss) trials is then seen as potentially perception related. However, recent studies found that report-related activity spreads throughout the brain, calling into question to what extent such tasks conflate perception-related activity with report-related activity. To isolate perception-related activity, we developed two paradigms in which the same mice were trained on both a regular (stimulus-go) contingency and a reversed (no-stimulus-go) contingency, in which they reported the absence of a whisker stimulus. By comparing no-report trials across the contingencies, we located perception-related activity within a posterior network of cortical regions in both cortices, most prominently in the retrosplenial cortex. This activity was on average an order of magnitude lower than report-related activity. In summary, our study revealed the mouse cortical areas associated with the perception of a stimulus independently of a perceptual report.

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A highly conserved A-to-I RNA editing event within the glutamate-gated chloride channel GluClα is necessary for olfactory-based behaviors in Drosophila

Galit Shohat-Ophir, *Bar Ilan University*

A-to-I RNA editing is a cellular mechanism that generates transcriptomic and proteomic diversity, which is essential for neuronal and immune functions. It involves the conversion of specific adenosines in RNA molecules to inosines, which are recognized as guanosines by cellular machinery. Despite the vast number of editing sites observed across the animal kingdom, pinpointing critical sites and understanding their in- vivo functions remains challenging. Here we study the function of an evolutionary conserved editing site in Drosophila, located in glutamate-gated chloride channel (GluClα). Our findings reveal that flies lacking editing at this site exhibit reduced olfactory responses to odors and impaired pheromone-dependent social interactions. Moreover, we demonstrate that editing of this site is crucial for the proper processing of olfactory information in projection neurons. Our results highlight the value of using evolutionary conservation as a criterion for identifying editing events with potential functional significance and paves the way for elucidating the intricate link between RNA modification, neuronal physiology, and behavior.

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Session A5

Chair: Arseny Finkelstein, Alon Rubin

Using large cellular populations to reveal the neuronal code

THE DISTRIBUTED CODE OF GOAL DIRECTED BEHAVIOR

Yael Bitterman, *The Hebrew University of Jerusalem*
Julien Courtin, Neurocentre Magendie, Bordeaux Andreas Luthi, The Friedrich Miescher Institute for Biomedical Research, Basel

To guide goal-directed behavior, widely distributed brain networks integrate sensory information with cognitive and action selection processes on a broad spectrum of temporal scales. However, it remains unclear how specific computations are distributed and whether systematic differences exist between brain areas. Here, we analyzed calcium imaging data collected from the basolateral amygdala, medial prefrontal cortex, and orbitofrontal cortex while mice performed a self-paced instrumental task. Combining latent state modeling with discrete series analysis we employed a data driven approach to extract interpretable structures directly from the high dimensional neuronal activity. We show that within all three nodes implicated in the control of behavior, the seemingly complex population activity was comprised of repeatedly used, stereotyped dynamical motifs, probabilistically sequenced, and organized in a nested hierarchy. The compositional hierarchy of these dynamics matched the modular task structure, from execution of fine-grained behaviors (seconds), to switches in the animals' motivational state (minutes). Through geometric analysis of the latent dynamics in neuronal space, we identified specificities in the representational maps across the network, with implications to the distributed functions that underlie adaptive behavior.

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DECOMPOSED LINEAR DYNAMICAL SYSTEMS (DLDS) FOR STUDYING NEURAL DYNAMICS WITHIN & BETWEEN BRAIN AREAS

Noga Mudrik, *Biomedical Engineering and Kavli Neuroscience Discovery Institute, The Johns Hopkins University*
Eva Yezerets, Biomedical Engineering, The Johns Hopkins University Yenho, Chen, Biomedical Engineering, Georgia Institute of Technology Ryan, Ly, Lawrence Berkeley National Laboratory Christopher, Rozell , Electrical and Computer Engineering, Georgia Institute of Technology Oliver, Ruebel, Lawrence Berkeley National Laboratory Adam Charles, Biomedical Engineering and Kavli NDI, The Johns Hopkins University

Learning interpretable representations of neural dynamics is a crucial step into understanding how recorded neural activity relates to behavior. However, existing models often overlook the non-stationary and non-linear behavior observed in real-world neural data, focusing instead on simplified projections or explicit dynamical systems. Here, we propose a decomposed Linear Dynamical Systems (dLDS) approach to capture these complex dynamics by representing them as a sparse time-varying linear combination of interpretable linear dynamical components. dLDS is trained using an expectation maximization approach where the obscured dynamical components are iteratively inferred using a dictionary learning procedure. This approach allows us to identify overlapping circuits, while the sparsity applied during the training maintains the model interpretability. We demonstrate that dLDS successfully recovers the underlying linear components and their time-varying coefficients in both synthetic and neural data examples. We also show that dLDS can capture smooth transitions between dynamical modes and learn efficient representations of complex data. By leveraging the rich data from the International Brain Laboratory (IBL) Brain Wide Map dataset, we model the communication of ensembles between and within brain regions and reveal task-related interactions that evolve over time—providing valuable insights into the mechanisms underlying information transfer in the brain.

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Cracking the social code using whole-brain recording of the larval zebrafish

Lilach Avitan, *Hebrew University of Jerusalem* Imri Lifshitz, Hebrew University of Jerusalem

To survive and reproduce, animals rely on the ability to maintain social interactions with specifics. These interactions are observed across various species, and the underlying neural circuits are largely conserved across all vertebrates. Nevertheless, little is known about the neural mechanism that integrates sensory information and transforms it into social actions. To address this question, we recorded whole-brain neural activity from a focal head-fixed and tail-free larval zebrafish observing a freely swimming conspecific simultaneously with high-speed behavioral recording of both fish. Neural responses cover the entire social cognitive process; from the sensation of the social cue, via evidence accumulation, the decision to act or not upon the cue, and finally the execution of a social action. Inspections of the neural manifold formed before the decision to act provide insights into the neural processes before social vs. nonsocial actions and suggest a circuitry account for the natural inter-individual variability of social levels.

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Internal structure of neuronal codes for space in hippocampus and cortex

Alon Rubin, *Department of Brain Sciences, Weizmann Institute of Science*

Recent advances in electrophysiology and optical imaging technologies enable the simultaneous recording of hundreds to thousands of neurons. As neural coding, computation, and communication likely depend on coordinated activity patterns across large cell populations, such data facilitate the study of the global structure of neural function, which cannot be unveiled by analyzing functional attributes at the single-neuron level. Specifically, rather than examining neuronal function at the single-cell level, modern rich datasets allow us to consider ensembles of neurons as populations and explore how their coordinated activity unfolds across space and time. Mapping these population responses as high-dimensional trajectories in an abstract activity space unveils the brain's capacity to encode information within complex patterns of neural firing. This perspective offers insights into emergent properties, such as collective computations and network states, as well as how they might lead to higher-order functions like memory and spatial cognition.

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Multi-regional and local mechanisms of cortical communication during goal-directed behavior

Arseny Finkelstein, *Tel Aviv University*

Regulation of information flow in the brain is critical for many forms of behavior. In the first part of my talk, I will focus on information flow within the frontal cortex microcircuitry and present a new all-optical method for rapid mapping of local connectivity in vivo. Combining connectivity mapping with a novel paradigm of mouse naturalistic behavior revealed functional connectivity motifs in the frontal cortex and the existence of neurons that function as network hubs, which had an unexpectedly high number of connections and a strong influence on neighboring neurons. Finally, I will show that analyses of interactions between 1,000,000 neurons, recorded simultaneously across multiple cortical areas, revealed a hitherto unknown organization of cortical population dynamics and communication patterns across brain regions. Taken together, these results pave a road to study how neuronal interactions on different spatial scales give rise to behavior.

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Brain wide network within and between naturally socializing mice

Odeya Marmor, *Medical Neurobiology department, Hebrew University*
Renana Terner, Medical Neurobiology department, Hebrew Univesity Vivian Khoury, Medical Neurobiology department, Hebrew Univesity Ariel Gilad, Medical Neurobiology department, Hebrew University

Social interaction is one of the crucial and versatile human abilities, enabling us to live in society. Growing evidence indicates that the social domain is primarily a complex network function rather than region specific. To better understand the social brain network, we use a novel state-of-the-art multi-fiber method to measure the brain-wide network as mice engage in freely moving and natural social interactions. This method enables us to chronically and simultaneously record neuronal activity from 24 recording sites brain-wide of two interacting mice. These areas include social related areas such as the prefrontal cortex, amygdala, ventral striatum, hippocampus, thalamus and more. Our results of three groups of mice (5 mice in each group), show that social engagement strongly activates the social brain areas, and that network connections differ between social interaction and non-social activity. Furthermore, we show that inter brain synchrony increases during social interaction while the intrabrain network decreases. The interbrain correlations further correspond to the social rank. These results will promote the understanding of underling brain wide networks during social interactions.

Session A6

Chair: Ofer Yizhar

Beyond "adult male mice": circuits and behavior throughout the lifespan

Tracing life's arc through behavior

Dana Rubi Levy, *Department of Neurobiology, Harvard Medical School, Boston MA*
Winthrop Gillis, Department of Neurobiology, Harvard Medical School, Boston MA
Rockwell Anyoha, Department of Neurobiology, Harvard Medical School, Boston MA
Nigel Hunter, Department of Neurobiology, Harvard Medical School, Boston MA
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Animals exhibit age-specific motor patterns. However, whether behavioral trajectories continuously change across lifespan or crystallize during specific developmental time points remains unknown. Here we provide the first systematic characterization of the ontogeny of vertebrate behavior from weaning till death. We find, using an ethologically inspired behavioral characterization algorithm, that behavior changes continuously and systematically throughout life. Mice exhibit a stereotypical "behavioral clock" that can predict age within days-to-weeks. However, the rate of behavioral evolution is dynamic: the motor repertoire of juvenile mice is similar across individuals but changes rapidly over time until puberty when the rate of change significantly drops. In late adulthood the change rate drops further, while the ability to predict individual identity significantly rises. When mice age, motor repertoires consolidate further into consistent, stereotypical, behavioral patterns. Male and female behavior followed distinct trajectories, as female behavior is more stable across life and exhibit a higher degree of inter-individual similarity. These results provide a unique platform for understanding the arc of species-, sex- , and individual-specific behavior and introduces a framework for studying the dynamic organization of motor circuits supporting action selection.

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Oxytocin signaling regulates maternally directed behavior during early life

Daniel ZELMANOFF, *Dept. of Brain Sci., Weizmann Inst. of Sci., Rehovot*
Menachem KAUFMAN, Dept. of Brain Sci., Weizmann Inst. of Sci., Rehovot, Israel Julien DINE, Dept. of Brain Sci., Weizmann Inst. of Sci., Rehovot, Israel Anna LITVIN, Dept. of Brain Sci., Weizmann Inst. of Sci., Rehovot, Israel Jonas WIETEK, Dept. of Brain Sci., Weizmann Inst. of Sci., Rehovot, Israel Ofer YIZHAR, Dept. of Brain Sci., Weizmann Inst. of Sci.

Oxytocin (OT) has been shown to play an essential role in the regulation of various social behaviors. Little is known, however, about its involvement in social behavior during early life. We set out to explore the role of OT in mother-infant interaction. Our results show that the activity of paraventricular OT neurons was increased by a 3-hour period of maternal separation (MS) and returned to baseline after reunion with the dam and littermates. Behaviorally, we found that acute MS increased the emission of USVs and maternally directed behavior upon social reunion. These effects were attenuated by applying an OTR antagonist during MS, suggesting that OT release during MS is important for this behavior. To investigate the role of OT release with higher spatial and temporal precision, we established an optogenetic protocol for noninvasive transcranial photoinhibition in freely behaving pups using eOPN3. Using this approach, we found that optogenetic silencing of OT neurons during MS alters USV emission patterns during separation and disrupts the correlation with vocal behavior upon reunion. In summary, our findings reveal an important role of OT in experience-dependent social behavior in pups, opening exciting opportunities for mechanistic understanding of neural circuits in the early postnatal period.

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The dynamic structure of behavioral individuality across developmental timescales

Shay Stern, *Technion*

Patterns of behavior across development are formed at multiple timescales, from typical movements over seconds and minutes to patterns of behavior that span the lifetime of the organism. The basic building blocks that characterize the individual's behavior across these long timescales are changes in its posture, reconstructing both stereotypic movements that are shared by individuals, as well as unique behavioral modes which define the individual-specific behavioral space. Here, we use unsupervised classification for extracting the complete dynamic structure of C. elegans behavioral individuality, by using long-term monitoring of posture dynamics of individual animals, across their developmental trajectory. Our dataset includes over 3000 individuals imaged at 3fps for days of measurements, from which we extracted ~1.7 billion body postures across time. This unique dataset defines a long-term behavioral space of an organism across all life-stages, at the population and individual level. We performed dimensionality reduction of posture dynamics modes to characterize differences in low-dimensional representations of behavioral spaces among individuals and to dissect the plasticity of individuality structures within tens of populations subjected to neuromodulatory and environmental perturbations. These results demonstrate the representation and unsupervised analyses of individual-specific behavioral signatures in the context of variable neuromodulatory and environmental states.

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Behavioral and neuronal signatures of adolescence in the mouse auditory cortex

Benne Praegel, *The Hebrew University of Jerusalem*
Adria Dym, The Hebrew University of Jerusalem
Adi Mizrahi, The Hebrew University of Jerusalem

Adolescence is known to be a period of uncertainty, exploration, and learning. Our understanding of the underlying neural correlations of adolescence remains scarce. Here, we studied adolescence through the prism of auditory learning, and the neural representations of learned sounds in the auditory cortex of mice. We asked whether adolescent and adult mice discriminate with tone categories differently, and how are these differences expressed in auditory cortical responses in behaving mice. First, we trained freely behaving mice to perform a go no-go task of pure tone categories. We reveal weaker performance in adolescence compared to adulthood and found that it was attributed to specific biases. Second, we trained head-restrained mice on the same task and performed two separate experiments: 1) We manipulated auditory cortex on a trial-by-trial basis using optogenetic silence. Inhibiting auditory cortex in adult mice decreased performance, indicating a causal relationship between auditory cortex and tone categorization. 2) We recorded single units in the auditory cortex during engaged behavior using neuropixels. We are currently evaluating the task-, stimulus- and choice-related activity in single neurons, as well as in population dynamics. Our aim is to reveal the neural correlations of behavior in adolescence as compared to adulthood.

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The afternoon role of the circadian VIP neurons in regulating the mammalian estrous cycle

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Jet lag and shift work have been found to disrupt the menstrual cycle and reduce fertility. To shed light on this issue, our study focuses on the role of vasoactive intestinal peptide (VIP) neurons, which display immediate responses to light and directly connect to gonadotropin-releasing hormone (GnRH) neurons responsible for regulating reproductive hormones. To investigate the dynamics, we recorded bulk GCaMP6s signals from SCNVIP neurons in live mice over days. Utilizing machine learning classifiers, we successfully distinguished between different estrous cycle days during the late afternoon. Furthermore, in standard lighting conditions, females ovulated every 4-5 days, but at near-complete darkness, ovulation decreased to every 7-8 days. By providing one hour of light in the late afternoon or activating SCNVIP neurons through chemo genetics, we were able to rescue the reduced ovulation rate. Through gene editing, we downregulated VIP receptors on GnRH neurons, resulting in a disruption of estrous cycle regulation, and the beneficial effect of late afternoon light exposure was lost. In conclusion, our findings suggest that the time-of-day-dependent activity of SCNVIP neurons is crucial for maintaining estrous cycle regularity and directly connecting light information to GnRH neurons, important information to improve fertility issues caused by disturbances in circadian rhythms.

Session B1

Chair: Abigail Livny-Ezer

The use of Artificial Intelligence (AI) in medical neuroimaging, will it change practice?

DIAGNOSIS, OUTCOME PREDICTION AND PRECISION MEDICINE IN BRAIN DISORDERS USING CONNECTOMICS AND AI.

Abigail Livny, *Division of Diagnostic Imaging, Sheba Medical Center*
Reut Raizman, Division of Diagnostic Imaging, Sheba Medical Center Tim Buchbinder, Division of Diagnostic Imaging, Sheba Medical Center Mayan Harel, Division of Diagnostic Imaging, Sheba Medical Center Yael Golan, Division of Diagnostic Imaging, Sheba Medical Center Anat Leibovici, Division of Diagnostic Imaging, Sheba Medical Center Galia Tsarfaty,Division of Diagnostic Imaging, Sheba Medical Center Aleksandra Plavsic, Head Trauma Rehabilitation Department, Sheba Medical Center Revital Amiaz, Department of Psychiatry, Sheba Medical Center

Introduction: In the field of neuropathology, especially in psychiatric and some neurological diseases, there is a lack of objective tools for diagnosis, prognosis and personalization of treatment. We used multimodal connectivity with artificial intelligence (AI) to identify biomarkers associated with brain disorders, cognitive outcomes and personalized treatment in two disorders.
Methods: Forty-nine concussed patients and 42 healthy controls, as well as 48 MDD patients and 48 healthy controls underwent structural (Diffusion Tensor Imaging) and functional (resting-state fMRI) imaging, along with cognitive assessments and treatment follow-up. Personalized multimodal connectomes were constructed and entered specific classification and prediction AI models.
Results: We reached an accuracy of 90% in diagnosis of MDD patients and of 84% accuracy in distinguishing concussed patients from healthy controls. In addition, the multimodal connectome classified treatment response to SSRIs with 83% accuracy. An association between connectivity measures and working memory was found in the concussed patients.
Conclusions: Our results demonstrate the ability to objectively diagnose patients with MDD and concussion, over and beyond the current subjective clinical practice. We conclude that the connectome harbors central information linked to clinical and cognitive outcome, suggesting its potential to evolve into an objective and personalized diagnostic and prognostic tool.

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Augmenting multi-modality neuroimaging in patients with brain tumors using ECOG, fMRI and AI

Yaara Erez, *Bar-Ilan University*

Objectives: Neuroimaging is widely used in clinical practice; nevertheless, currently available techniques are limited in providing patient-tailored treatment and prognosis. I will demonstrate how multi-modality neuroimaging leveraged by AI approaches can be used for developing personalized treatment for patients with brain tumors. I will focus on executive control – cognitive processes such as attention, planning and problem solving, which are often impaired in patients.

Methods: We used fMRI in healthy participants to identify the frontoparietal control network in individuals. Within a precision neuroimaging approach, we collected extensive per-patient multi-modality data from patients with glioma. We used electrocorticography (ECOG) during awake surgery to identify critical functional regions, aimed at preventing cognitive deficits post-surgery.

Results: The frontoparietal network was reliably identified in healthy individuals, generalizing across tasks. Using ECOG in patients, we identified an electrophysiological signature of the control network, which distinguished frontal control regions from adjacent networks. Further integrating ECOG and pre-surgery resting-state fMRI at the individual level, connectivity patterns revealed that tumor-infiltrated cortex participates in large-scale cognitive circuits, also linked to cognitive outcome.

Conclusions: Our findings demonstrate the opportunities and challenges of using multi-modality precision neuroimaging and AI for advancing personalized treatment and the understanding of disease progression.

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Leveraging Artificial Intelligence for Advanced Neural Prosthetics: Enhanced Detection of Dexterous

Firas Mawase, *Technion*

Neural prosthetics provide a lifeline to individuals who have lost limbs or suffer from paralysis, enabling a degree of function and self-sufficiency that might otherwise be unattainable. The urgent need for advancements in this field, specifically those facilitating more precise and dexterous hand movements, is the driving force behind our research. Existing neural prosthetic solutions, which are primarily based on electromyography (EMG) signals, face significant limitations due to the inevitable deterioration of these signals over time. Our study proposes an innovative approach to address these limitations by harnessing the power of artificial intelligence (AI) to decode electroencephalography (EEG) signals and data from inertial measurement units (IMUs) located at the elbow and shoulder. We focused specifically on event-related potential (ERP), frequency responses and motion activity (angular positions and velocities) during the movement preparatory period. By implementing this methodology, we have achieved an 80% enhancement in the detection of grasp movements. Additionally, we'll discuss the success rate of detecting various types of movements and hand orientations, providing a comprehensive overview of our achievements in this field. Our preliminary findings strongly indicate that our approach could significantly augment the performance and functionality of neural prosthetics, offering promising possibilities for future advancements.

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PREDICTING COGNITIVE ABILITIES FROM BRAIN CONNECTIVITY USING ARTIFICIAL INTELLIGENCE

Maya Kadushin, *Faculty of Medicine and Sagol School of Neuroscience, Tel Aviv University*
Ido Tavor, Faculty of Medicine and Sagol School of Neuroscience, Tel Aviv University.

Objectives Individuals highly differ in their cognitive skills and learning abilities. Functional connectivity patterns, derived from functional magnetic resonance imaging (fMRI), have been shown to predict individual traits. Although, these traits are often evaluated under laboratory-constrained settings rather than real-life. Here, we examined the predictability of real-life academic scores from functional connectivity using artificial intelligence (AI).

Methods Brain connectivity patterns were extracted from the fMRI data of 379 participants who underwent an MRI scan as part of The Strauss Neuroplasticity Brain Bank (SNBB), Tel Aviv University. Connectivity patterns were utilized to predict participants' global and domain-specific (e.g., verbal, math) academic scores. Prediction accuracy was calculated as the Pearson's correlation coefficient between actual and predicted scores.

Results Real-life academic scores were successfully predicted from functional connectivity patterns. We found that global scores were predicted from wide-spread brain-connectivity, whereas specific skills (i.e., math and verbal scores) were predicted by more segregated connections.

Conclusions Real-life learning abilities can be predicted from brain connectivity patterns using AI, suggesting these patterns may be used as an objective biomarker of real-life cognitive ability and possibly assist in early detection of cognitive decline.

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Does AI provide new information or validate existing findings? Current and future directions in dyslexia

Tzipi Horowitz-Kraus, *Associate Professor Educational Neuroimaging Group Faculty of Education in Science and Technology Faculty of Biomedical Engineering Technion-Israel Institute of Technology*
Associate Professor (PAR) Neuropsychology Department, Kennedy Krieger Institute Department of Psychiatry and Behavioral Sciences, Johns Hopkins School of Medicine Baltimore, Maryland, USA.

Reading difficulty (RD, or dyslexia) is a multifacet disorder characterized by slow and/or inaccurate reading and/or reading comprehension challenges. The sources underlying RD range from language/phonological difficulties to decoding and word recognition to executive function (EF) challenges. In a series of studies, we aimed to define the involvement of EF, visual and auditory networks in word reading and reading fluency in children with RD using neuroimaging (EEG, functional MRI) and behavioral/cognitive measurements. Then, the effect of EF utilization during reading remediation was determined. Finally, machine learning (ML) algorithms and resting state data were used to determine the neurobiological characteristics of RD without an apriori hypothesis. Results showed specific neurobiological characteristics associated with EF alterations in RD. EF-based reading intervention increased EEG amplitudes and functional connections during both reading and resting-state conditions within the cingulo-opercular network and between the visual processing and the cingulo-opercular networks found in RD. Applying ML verified the involvement of EF and sensory networks in RD, confirming our hypothesis-driven approach. The role of EF in reading in RD, in particular as a possible “synchronizer” of reading-related systems and using AI methods to predict the gain from interventions, will be discussed.

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Session B2

Chair: Benedetta Heimler

Cognitive-motor-affective interactions during naturalistic behaviors in virtual reality

HARNESSING THE FULL POWER OF NATURALISTIC PARADIGMS FOR THE STUDY OF HUMAN BEHAVIOR

Michal Ramot, *Weizmann Institute of Science*

In recent years there has been a shift towards using more naturalistic paradigms in research, driven by the understanding that standard controlled lab experiments fail to capture the full range of both experience and responses. This is especially relevant in human studies, where the behaviors we are interested in measuring are particularly complex. Yet the very complexity of naturalistic paradigms which makes them interesting, also makes them difficult to study. How can we balance the benefits of naturalistic paradigms with the necessity for robustness, reliability, and the isolation of variables in our measurements? I will discuss a few paradigms in which we use the full range of naturalistic behavioral experimentation techniques – virtual reality, movie watching, eye tracking, gait, physiological recordings – coupled with fMRI measurements, to ecologically study a wide range of human behaviors. Our focus is on individual differences, whether we are studying spatial navigation, social cognition or anxiety, and I will discuss some of the many challenges which are shared in studying these different domains, and how we have approached them.

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Exploring Unconscious Processing with Immersive Virtual Reality

Rony Hirschhorn, *Sagol School of Neuroscience Tel Aviv University*

Unconscious processing has been mainly studied using lab-based psychophysical manipulations (e.g., masking, continuous flash suppression, binocular rivalry) and 2D stimuli. Do findings obtained in traditional paradigms generalize to the unconscious processes that operate in real-life situations outside the laboratory? We developed a novel, ecological way to probe unconscious processing in an immersive virtual reality environment (VR), using multi-trial inattentional blindness (IB). In our paradigm (VRIB), salient stimuli are embedded in a naturalistic urban environment while participants are engaged in a demanding task. In this talk, we will present results demonstrating that the VRIB paradigm effectively suppresses stimuli from awareness - allowing us to examine the question of high-level unconscious processing in naturalistic contexts. Then, we will show how the VRIB paradigm can be used to study the unconscious processing of phobic and non-phobic stimuli. We will present both behavioral and physiological recordings (gaze, heart rate, and skin conductance), and discuss the trade-offs between using ecological measurement tools and ensuring accurate measurements that lead to statistically meaningful results.

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Quantifying Apathy Through Virtual Reality: A Novel Physiological Approach Using Gaze and Autonomic Measures

Ramit Ravona- Springer1,2,3, Or Koren4, Noam Galor4, Michal Lapid2,5, Yotam Bahat4, Ronen Fluss6, Meytal Wilf4, Shlomit Zorani2,3, Michal Schnaider Beeri7, Meir Plotnik4,8,9

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8 Department of Physiology and Pharmacology, Faculty of Medicine, Tel Aviv University, Israel;
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Objectives: Apathy, a multifaceted disorder of motivation, encompasses emotional, cognitive, and behavioral components. It serves as a robust predictor of cognitive decline, dementia conversion, and accelerated disease progression. By limiting engagement in brain-healthy activities, apathy may further exacerbate cognitive deterioration. Its association with Alzheimer's Disease and Related Disorders (ADRD) pathology positions apathy as a potential behavioral marker and treatment target for ADRD. Current apathy assessment tools are hampered by subjective biases, symptom overlap, and difficulties in evaluating distinct components, underscoring the need for more objective and comprehensive evaluation methods.

Aims: To develop an objective tool for quantifying apathy.

Methods: The study involved 97 participants (67 with cognitive impairment [CI] and 30 cognitively normal [CN]; mean age 74.3±6.2 years, 56.7% female). Subjects were

exposed to various emotional and cognitive stimuli in a virtual reality (VR) environment. Measurements included gaze metrics (time to first fixation [TTFF] and total fixation duration [TFD]) and autonomic nervous system (ANS) reactivity (heart rate, galvanic skin response [GSR], and respiration). Apathy was clinically assessed using the Lille Apathy Rating Scale (LARS) short version, with a cutoff of ≥-7 defining apathy. Depression was evaluated using the 15-item Geriatric Depression Scale (GDS), with a cutoff of ≥5 indicating depression.

Results: The sample comprised 14 participants with apathy only, 9 with depression only, 10 with both conditions, 63 with neither, and 1 with incomplete data. For all emotional stimuli, apathy-only participants demonstrated longer TTFF (p=0.039, ES=0.798) and shorter TFD (p=0.023, ES=0.578) compared to those without apathy or depression. Higher LARS scores correlated with shorter gaze duration at positive emotional stimuli (rs=-0.234, P=0.032) and reduced TFD for both congruent (r=-0.244; p=0.031) and incongruent (r=-0.224; p=0.048) cognitive stimuli. No significant association was found between ANS reactivity and apathy.

Conclusions: Apathy is associated with decreased gaze engagement in response to both emotional and cognitive stimuli.

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More than meets the eyes – gait modulations due to gravity

Meir Plotnik, *Center of Advanced Technologies in Rehabilitation, Sheba Medical Center, Ramat Gan, Department of Physiology and Pharmacology, Faculty of Medicine, Tel Aviv University, Sagol School of Neuroscience, Tel Aviv University*

Objectives: Using virtual reality (VR) technology, we studied the role of vision in modulating gait when transitioning to inclined walking.

Methods: Young (n=43; 26.8 ± 3.9 years; 22 females) and older adults (n=15; 68.93±4.17 years, 7 females) walked in a large-scale VR system on a self-paced treadmill synchronized with projected visual scenes, while being randomly exposed to a range of inclinations (−15◦ to +15◦). Incongruent transitions consisted of a physical-visual mismatch (e.g., treadmill leveled & visual scene uphill).

Results: For both age groups, visual-only (virtual) inclinations induce consistent locomotor adaptations to counter expected gravity-based changes: downhill virtual inclinations activate the braking effect in anticipation of a gravitational boost, whereas uphill virtual inclinations promote an exertion effect in anticipation of gravitational deceleration. We observed linear relation between the relative change in gait speed and the anticipated gravitational forces associated with the virtual inclinations (E.g., gait speed increase of ∼7%, ∼11%, and ∼17% in response to uphill virtual inclinations of +5^{o}, +10◦, and +15◦, respectively). Visually induced gait modulations were highly correlated with visual dependency test scores obtained at baseline.

Conclusions: Our results highlight the prominent role of vision in modulating our perception of gravity and related consequences on locomotion.

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Evaluating cognitive-motor interactions in Parkinson's disease using a novel VR-based assessment

Benedetta Heimler, *Center of advanced technologies in rehabilitation (CATR), Sheba Medical center Meytal, Wilf, Weizman Institute of Science*, Shani Kimel-Naor, Center of advanced technologies in rehabilitation (CATR), Sheba Medical center Noam, Galor, Center of advanced technologies in rehabilitation (CATR), Sheba Medical center Amichai, Gottlieb, Sagol School of Neuroscience, Tel Aviv University Meir, Plotnik, Center of advanced technologies in rehabilitation (CATR), Sheba Medical center.

Objectives: Investigate the efficacy and advantages of innovative virtual-reality (VR)-based cognitive-motor evaluations on persons with Parkinson's Disease (PwPD).

Methods: 22 PwPD and matched controls performed two versions of a classic executive functions' test, the color-trails-test (CTT): the typical pen-and-paper (P&P)-CTT and our novel, and previously validated, VR-CTT. In the P&P-CTT, participants draw lines connecting numbered targets in ascending order (Trail A), and while also alternating between colors (Trail B). This yields a single outcome measure, i.e., completion times. In our novel VR-CTT, the test is carried-out in a virtual 3D space requiring participants to perform full-range arm movements to connect virtual target balls, thus capturing more complex motor-cognitive profiles.

Results: PwPD showed medium-sized significant correlations between P&P and VR-CTT completion times (Trails A: rho=0.4 for; Trails B: rho=0.5) and resulted overall significantly slower than controls (p=0.003). Kinematics analyses on VR-CTT performances showed that PwPD compared to controls displayed significantly slower target-to-target hand trajectories, and significantly longer lags between head rotations and hand motor execution (p=0.04), reflecting delayed synchronization between motor effectors.

Conclusions: These results highlight the benefits of thoroughly characterizing motor kinematics components within cognitive evaluations, ultimately contributing to the further understanding of cognitive-motor interactions.

Session B3

Chair: Dan Frenkel

Impairment in metabolic pathways in neurodegenerative disease

ABCA TRANSPORTERS MODULATE ESSENTIAL METABOLIC PATHWAYS AND PROTECT AGAINST NEURODEGENERATION

Prof. Dr. Dr. Jens Pahnke, MD/PhD/EFN - 1,2,3,4 www.pahnkelab.eu 1*) University of Oslo, Oslo University Hospital - Department of Neuropathology Research / Department of Pathology 2) University of Lübeck, University Medical Center Schleswig-Holstein - Computational Biology and Chemical Biology Lab 3) University of Latvia - Department of Pharmacology 4) University of Tel Aviv - Department of Neuroscience*

The ABC transporters A1 and A7 have been described as genetic risk factors of Alzheimer's disease in 2011 (Hollingworth et al.) and 2022 (Holstege et al.), long after the description as disease modulators in animal and cell models (since 2003 by several groups). We have been investigating the effects of ABC A transporters in Alzheimer's disease (APPPS1 model - Radde et al. 2006, EMBO) and Huntington's disease (our new zQ175dn model - Wu et al. 2022, IJMS) and discovered essential regulatory effects on lipid and lipid-soluble hormones. Additionally, we investigated libraries of compounds using computational chemistry and chemical biology analyses to detect modulators of ABC A1/7 transporters. We discovered and tested compounds in cell culture assays related to steroid hormone signaling to be binders and inhibitors to ABC A1/7 transporters. Several steroid hormones modulate essential metabolic pathways and are needed to keep the body AND brain in an anabolic metabolic state. Anabolism is needed to form and rebuild synapses, to keep degradation of waste peptides working and to remodel connections in the brain - functions needed to cope with neurodegeneration. Furthermore, sex-related differences in the prevalence of neurodegenerative diseases could be explained by differences in steroid hormone signaling.

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Impaired autophagy in apoE expressing cells

Pinkas-Kramarski Ronit, Simanovich Shira, Michaelson Daniel, Nechustai Lior, Bassel Rawan, Solomon Shira, Frenkel Daniel and Schmukler Eran, *Tel-Aviv University*

Autophagy, a process of self-degradation and turnover of cellular components, controls the number of surviving cells and has become a focus in neurodegenerative disorders including Alzheimer's (AD) and Parkinson's diseases. Beclin1, a Bcl-2 interacting protein was previously found to promote autophagy and to have a BH3-like domain which interacts with the Bcl-2 anti-apoptotic proteins to inhibit autophagy. In our studies we demonstrated that autophagy is induced following neurotrauma as a protective mechanism. The Apolipoprotein E4 allele (APOE4) is a major genetic risk factor for sporadic Alzheimer's disease; however, the mechanisms by which it affects disease progression and exerts its pathological effects are still unknown. Recently, we have shown that autophagy is impaired in APOE4 compared to APOE3-expressing glial cells. We also found differences between APOE3 and APOE4 expressing cells in mitochondrial network dynamics, including fusion, fission and mitochondrial network dynamics. Our results indicate the impairment of several mitochondrial functions in APOE4-expressing cells. Importantly, the autophagy inducer rapamycin enhanced mitophagy and improved mitochondrial functioning. Collectively, the results demonstrate that APOE4 expression is associated with altered mitochondrial dynamics, which might lead to impaired mitochondrial functions. This, in turn, may contribute to the pathological effects of APOE4.

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Mitochondria repair in Huntington's disease

Hagit Eldar-Finkelman, *Tel Aviv University*

In previous work, we showed that GSK-3 is a negative regulator of autophagy, lysosome, and endocytosis networks. We suggested that GSK-3 impairs metabolic homeostasis that, in turn, contributes to the accumulation and aggregation of neurotoxic proteins such as the mutant huntingtin (mHtt), a major hallmark of Huntington's disease (HD). Here we investigated the specific roles of GSK-3 isozymes, a or b, in regulating mHtt dynamics, and mitochondria activity under oxidative stress conditions. Our results indicated that GSK-3a plays a dominant role in regulating mHtt dynamics as observed in cultured cells and in primary neurons. Overexpression of GSK-3b (but not GSK-3b), accelerated the formation of mHtt aggregates, while its selective inhibition enhanced autophagic activity manifested by increased expression levels of beclin 1 and Wipi 1, and enhanced activity of cathepsin D. Nevertheless, GSK-3a could increase mHtt aggregates in autophagy-deficient cells as well. We found that GSK-3a increased cellular protein ubiquitination including mHtt ubiquitination which likely slowed down its proteasomal degradation. Under oxidative stress conditions, inhibition of mTOR, or GSK-3a recovered cells' viability by 30%, and improved mitochondria function. Collectively, our results point toward distinguished roles of GSK-3 isozymes in regulating metabolic homeostasis of aggregation-prone proteins and mitochondria function under oxidative stress.

Session B4

Chair: Ben Engelhard

Circuit mechanisms of motor learning and control in animals and humans

M1 reorganization of layer 2-3 network dynamics underlying motor learning

Hadas Benisty, *Department of Neuroscience Technion Medical School*
Amir Ghanayim, Department of neuroscience Technion Medical School Avigail, Cohen-Ramon, Viterbi Faculty of Electrical and Computer Engineering Technion Sivan, Schwartz, Department of neuroscience Technion Medical School Ronen, Talmon, Viterbi Faculty of Electrical and Computer Engineering Technion Jackie, Schiller, Department of neuroscience Technion Medical School

Learning, planning and execution of movement, are carried out by a highly complex and distributed system, with the primary motor cortex (M1) being the main output cortical region to downstream brainstem and spinal cord execution centers. Previous studies have shown that during motor learning M1 undergoes major plasticity changes at multiple levels, ranging from motor representations, dendritic computations, and branch spike properties. However, much less is known regarding the way motor related synaptic plasticity reshape network organizations, that in turn ultimately results in learning of new motor tasks. We recorded the activity of layer 2-3 Pyramidal Neurons (PNs) in M1 during learning of a hand-reach task. Animals demonstrated a steady improvement in motor execution of the task; success rate monotonically increased till saturated where all animals kept high level of proficiency. To explore changes in functional activity of the cellular network we developed a novel analysis approach to compare network dynamics throughout training. We find that motor learning is associated with gradual reorganization of the ensemble activity as it transforms from a naïve configuration toward a stable configuration. This is also true for the outcome related neurons we previously described where this population emerges and stabilizes during learning.

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Linking actions to their sensory consequences in the human brain

Roy Mukamel, Tel-Aviv University

Performance of goal-directed actions requires integration of motor commands with their expected sensory outcome. Nevertheless, the process by which the brain links actions to sensory consequences is poorly understood. A salient feature of motor and sensory circuits is their contralateral hemispheric bias, which might play a role in the integration process and affect learning of sensorimotor skills. Previous studies show that evoked responses in sensory regions are different if the evoking stimulus is the consequence of the perceiver's action, or the consequence of an external event. However, the functional significance of such motor-induced sensory modulations - are they a unique signature of agency ('I did it') or due to differences in outcome predictability - is unclear. During my talk I will describe a set of experiments, in which we manipulated the configural relationship between motor and sensory circuits engaged during learning of sensorimotor tasks. Our studies indicate that evoked responses in sensory regions contain a significant component of agency and even limb-specific information. Additionally, our results are in better agreement with an agent over a predictive account of sensory modulations and have implications for contemporary models of motor control.

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SPEECH FEATURES NEURAL ENCODING IN THE THALAMUS OF PARKINSON'S DISEASE AND ESSENTIAL TREMOR PATIENTS

Ariel Tankus, 1,2,3
Yael Lustig, 2 Guy Gurevitch, 4,5 Achinoam Faust-Socher, 6 Ido Strauss, 1,*2 1 Functional Neurosurgery Unit, Tel Aviv Sourasky Medical Center*.
2 Department of Neurology and Neurosurgery, Faculty of Medicine, Tel Aviv University, Tel Aviv. 3 Sagol School of Neuroscience, Tel Aviv University, Tel Aviv. 4 Sagol Brain Institute, Tel-Aviv Sourasky Medical Center, Tel-Aviv. 5 Department of physiology and pharmacology, Faculty of Medicine, Tel Aviv University, Tel Aviv. 6 Movement Disorders Unit, Department of Neurology, Tel Aviv Sourasky Medical Center, Tel Aviv.

Objectives: To find the encoding of speech features, in particular vowel phonemes, in the single neuron activity of the human left Ventralis intermediate nucleus (LVim) of the thalamus, during the production, perception and imagery of speech.

Methods: Intraoperative single-neuron LVim activity of 8 neurosurgical patients with PD or ET undergoing DBS implantation or RF lesioning was recorded while patients articulated, perceived, or imagined the five monophthongal vowel sounds.

Results: Single LVim neurons encode individual vowel phonemes during speech production, perception, and imagery. Their main encoding schemes are broad and sharp tuning, with a similar percentage of units each. Almost half of the broadly tuned units demonstrated sinusoidal tuning. PD patients had a lower percentage of speech-related units than ET patients in each aspect of speech, a significantly lower percentage of broadly tuned units, and a significantly lower median firing
rates during speech production and perception, but significantly higher rates during imagery.

Conclusions: Our findings explain, at the single neuron level, speech side effects caused by DBS and RF lesioning of the LVim. Moreover, they may indicate that speech-related units in the LVim of PD patients may be degraded even in the subclinical phase. Support: Israel Ministry of Science and Technology (Grant 17630).

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Striatal Circuits Underlying Sensorimotor Functions

Gilad Silberberg, *Karolinska Institutet, Stockholm, Sweden*

The integration of sensory information is modulated by the state of the animal (e.g. alertness) and ongoing behavior. Our previous studies have shown that striatal projection neurons (MSNs) in anesthetized mice integrate sensory inputs from both sides of the body and from different sensory modalities. However, it is not clear how these sensory responses are modulated by movement. To address this question, we obtained in vivo whole-cell recordings in the dorsolateral striatum of awake mice. We used the “optopatcher” to identify direct- and indirect pathway MSNs (dMSNs and iMSNs, respectively) in real-time during recordings. We found that both dMSNs and iMSNs exhibit sensory responses to whisker deflection and that these responses are attenuated by whisking. In addition, we show that dopamine depletion alters bilateral sensory responses.

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Session B5

Chair: Tal Laviv

Molecular mechanisms of synaptic plasticity in the developing and adult brain

Exploring the Interplay of Hippocampal TACR3 and Systemic Testosterone in the Regulation of Anxiety

Shira Knafo, *Ben-Gurion University of the Negev, Beer-Sheva*

This study explores the interplay between TACR3 expression, anxiety, sex hormones, and synaptic plasticity. Severe anxiety correlates with reduced TACR3 expression in the ventral hippocampus. In female rats, TACR3 expression fluctuates during the estrus cycle, indicating sensitivity to sex hormones. Notably, during sexual development, hippocampal TACR3 expression increases alongside elevated serum testosterone levels, coinciding with reduced anxiety. Additionally, reciprocal regulation exists between hippocampal TACR3 expression and serum testosterone levels. TACR3 significantly impacts synaptic function, influencing the PKC pathway, CaMKII activation, AMPA receptor phosphorylation, spine density, and synaptic connectivity. Rats with TACR3 deficiency demonstrate lower testosterone levels, heightened spine density, and impaired long-term potentiation (LTP) in the dentate gyrus. Functional TACR3 expression results in spine shrinkage, while a defective TACR3 increases spine density and size. Neurons expressing the defective TACR3 exhibit inadequate firing pattern responses to LTP induction, which can be rectified with testosterone treatment. These findings provide valuable insights into the intricate relationship among TACR3, sex hormones, anxiety, and synaptic plasticity, offering potential targets for therapeutic interventions in TACR3-related anxiety.

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The genomic basis of behavioral state-dependent modulation of sensory processing and neural circuit

Ivo Spiegel, *Department of Brain Sciences, Weizmann Institute of Science*

How do neural circuits maintain stable percepts and memories while at the same time being plastic enough to allow for learning of new skills and information? Since stability and plasticity are opposing forces in neural circuits, key questions in neuroscience concern the molecular and cellular mechanisms that maintain the functional stability in neural circuits while allowing for their learning-related plasticity. In my talk, I will discuss our recent findings on the genome's role in maintaining the functional stability of neural circuits via activity-induced gene expression and homoeostatic control over excitation/inhibition ratio (E/I ratio) and neural firing rates. I will also discuss a novel approach recently developed by us (2P-NucTag) that allows for in depth molecular and cellular analyses of functionally defined neurons in vivo and that holds great promise for dissecting the molecular and cellular mechanisms that control circuit stability and plasticity.

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Unraveling the Dynamics of MeCP2 in Neuronal Circuits: A Novel Approach Using 2pFLIM to Explore DNA Damage Response in Rett Syndrome

Sharbel Eid, *Tel Aviv University*
Michal Lapidot, Aviv Zaid-or Yossi Levi and Tal Laviv

Rett syndrome (RTT) is a postnatal neurodevelopment disease, RTT is caused by loss of function mutations in a single gene encoding for methyl CpG binding protein 2 (MeCP2). MeCP2 is an important epigenetic regulator highly expressed in the mammalian brain. MeCP2 tightly binds methylated regions across the genome, but it is still not clear what the precise physiological function of MeCP2 is in the brain. In this project, we propose to study the role of MeCP2 in the intact neural circuits of the normal brain by using new FRET/FLIM biosensors. Our Biosensor will monitor interactions of MeCP2 within it signaling complex to allow dynamic measurements as a proxy of its function at single-cell resolution. We were interested in the role of this complex following DNA double-strand breaks and damage, which has been previously shown to be an integral developmental aspect of the neuronal genome and MeCP2 has been suggested to participate in this process. These interactions are disrupted due to Rett syndrome mutations resulting in augmented DNA damage. We propose that a major role of MeCP2 is to regulate DNA damage repair, a function that is altered in Rett syndrome, and could propose a new therapeutic approach for Rett.

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Channeling Mitochondrial Calcium for Homeostatic Regulation of Hippocampal Activity

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Maxim Katsenelson(1,2)
Inna Slutsky (1)
1 *Tel Aviv University*, 2 Sagol School of Neuroscience, Tel Aviv University

Objectives: Homeostasis of neuronal activity is an absolute requirement for the healthy and functional brain. This study investigated the role of the mitochondrial calcium uniporter (MCU) in homeostatic regulation of mean firing rate (MFR) in the hippocampus.

Methods To evoke and monitor homeostatic responses in vivo, a novel method was developed to continuously administer pharmacological agents to CA1 while recording single unit activity over extended periods. This method was applied to transgenic mice lacking MCU in CA1 (CA1: MCU-KO). The effects of MCU deletion were also studied ex vivo using electrophysiological and imaging techniques.

Results: Deletion of MCU in hippocampal neurons inhibited mitochondrial Ca2+ influx evoked by high frequency spike bursts, without affecting cytosolic Ca2+ influx. In vivo, local application of the GABAB receptor agonist baclofen rapidly reduced CA1 MFR. In control mice, MFR gradually recovered to baseline levels within two days despite the persistent application of baclofen. No such homeostatic response occurred in CA1: MCU-KO mice.

Conclusions: This data shows that CA1 MFR is homeostatically regulated in response to inactivity, and that this regulation depends on MCU expression. These findings reveal fundamental principles of neuronal homeostasis and identify potential therapeutic targets for neurological disorders characterized by dysregulated MFR.

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The role of non-vesicular lipid transport at ER-PM contact sites in phosphoinositide signaling in early neuronal development

Charles Chia Te Chien, Alan Guo, Joanna Szczurkowska, Athena Choi, and Maya Shelly
Department of Neurobiology and Behavior, School of Medicine, Stony Brook University, NY

Phosphoinositide lipid signaling is implicated in many cellular functions and is crucial in embryonic neuronal development. PI(4,5)P2 is a key lipid at the plasma membrane (PM), mediating various signaling pathways downstream of secreted cues, directly downstream of PI(4,5)P2 or following its phosphorylation to PI(3,4,5)P3 (PIP3) by PI3-Kinase. PIP3 and Akt signaling are critically implicated in dendrite development, effects largely mediated via diffusible neurotrophins. Neurotrophins BDNF and NT-3 expression are elevated in dendrites during and play a critical role in dendrite growth and branching. PI(4,5)P2 homeostasis during receptor stimulation is main-tained by a cyclical metabolic pathway, phospha¬tidylinositol (PI) cycle. The PI cycle and the enzymatic machinery required to sustain it are spatially segregated between the ER and PM. In the developing brain, neurons are perpetually exposed to cues that trigger the use and hydrolysis of PM PI(4,5)P2. Developing neurons must accommodate rapid on-demand PI availability at targeted locations of PI(4,5)P2 signaling and turnover in response to external cues, during extensive morphogenesis in dendrite development. The slow and non-specific vesicular transport might not meet this demand. Recent evidence suggests that an alternative mode of lipid transport, by lipid transport proteins at ER-PM contact sites, may provide a localized, rapid on-demand replenishment of PM PI(4,5)P2 and drive its downstream signaling following its hydrolysis in response to external cues. ER is ubiquitously present in dendrites of early developing neurons. Thus, PM PI(4,5)P2 replenishment at ER-PM contacts might be

prominent during extensive morphogenesis in embryonic dendrite development. We determine whether a lipid transport protein is a critical regulator of PI(4,5)P2/PIP3 homeostasis at ER-PM contact sites, and in PI(4,5)P2/PIP3 signaling in dendrite development. The Phosphatidylinositol Lipid Transport Protein can provide precursors of PI(4,5)P2 to PM while also extracting PI(4,5)P2 metabolite PA from PM for PI synthesis in the ER, thus autonomously sustaining the PI cycle at localized regions of PI(4,5)P2 depletion. Furthermore, the lipid transport protein is recruited to PM only following PI(4,5)P2 hydrolysis. This makes the lipid transport protein an optimal candidate to accommodate rapid on-demand PI availability at targeted locations of PI(4,5)P2 signaling and turnover in response to external cues, in dendrite development. Using state-of-the-art genetic probes to track PI(4,5)P2 and PIP3 signaling, combined with cutting edge genetic approaches including acute gene overexpression and knockdown in utero, CRISPR-mediated genome editing, and highly localized manipulations of signaling, our study is designed to determine the role of the lipid transport protein in dendrite development in mouse developing cortical pyramidal neurons. The elaborate dendritic arbors of pyramidal neurons underlie synaptic connectivity. Disruption in dendrite development plays a causative role in many neurodevelopmental and psychiatric disorders, mental disability, epilepsy, Schizophrenia, Fragile X, and autism. Abnormal activity of Akt is associated with these pathologies and characterized by defects in dendrite development. Furthermore, the lipid transport protein is linked to human neuropathologies. By exploring the mechanistic basis of PI-signaling, our study will advance understanding of early molecular events in dendrite structural plasticity in principal neurons in the rodent brain and their implications in neurodevelopmental pathologies.

Session B6

Chair: Oded Rechavi

"Cogito, ergo sum" - how perception shapes our physiology

Psycho-behavioral and pharmacological stress-management interventions in cancer patients improve pro-metastatic molecular tumor characteristics

Shamgar Ben-Eliyahu, Oded Zmora, Steve W. Cole, Gil Goldzweig, Lee Shaashua, Rebecca Jacoby, Rita Haldar, Tsipi Hanalis-Miller, Eran Sharon, Nahida Sakis, and Itay Ricon-Becker
Tel Aviv University

Sympathetic, HPA, and inflammatory responses were shown to suppress anti-metastatic immunity, reduce the efficacy of immuno- and chemo-therapies, and accelerate perioperative cancer metastasis. To overcome such deleterious effects in cancer patients, we conducted three randomized controlled clinical trials (RCT) in breast (BC) and in colorectal cancer (CRC) patients, testing the efficacy of pharmacological and psycho-behavioral perioperative interventions. A 20-day perioperative pharmacological blockade of β-adrenergic and COX2 signaling (using propranolol+etodolac treatment), significantly improved molecular biomarkers of malignant and metastatic potential in both CRC and BC tumors, including reduced epithelial-to-mesenchymal transition (EMT); reduced tumor infiltrating monocytes; increased tumor infiltrating NK and B cells; and improved activity of several anti-metastatic transcription factors (TF). In CRC, treatment reduced 8-year recurrence rate from 50% to 12.5%, albeit insufficient study power. Importantly, in BC patients, we also developed and tested a perioperative 6-week individually-tailored psycho-behavioral stress-management intervention. The intervention improved activity of several tumor TF (e.g., STAT and GATA families), overlapping with the effects of the pharmacological intervention, and improved tumor biomarkers not affected by the

drug treatment, including glucocorticoid (GR) and inflammatory (NFkB) signaling, and tumor M1-macrophage polarization. These findings indicate the efficacy of this psycho-behavioral interventions in reducing pro-metastatic processes in the malignant tissue, and suggest potential synergisms with the pharmacological approach. The favorable biomarker indications in these RCTs, and the suggested improved long-term clinical outcomes, provide justifications for conducting larger perioperative psycho-behavioral and/or integrated pharmaco-behavioral RCTs in various cancer types. Such interventions could also improve immune- and chemo-therapies, especially in stress-inflammatory settings.

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The inspirational brain

Noam Sobel, *Weizmann Institute of Science*

The sense of smell dictated by a sniffing mammalian brain Olfaction depends on a sensorimotor process: sniffing. For there to be an olfactory percept, there must be a sniff. The sniff not only transports the stimulus, but it also primes the brain for stimulus arrival, triggering ensemble activity optimized for information processing. We put forth the hypothesis that because olfaction served as an evolutionary developmental template for the mammalian brain, sniff-dependent processing extended beyond olfaction alone. We argue that sniffs prime the brain for processing information of any kind, not only odor. I will present evidence for this hypothesis from experiments in humans in both health and disease.

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How beliefs shape reality: from information processing to physical health

Liron Rozenkrantz, *The Azrieli Faculty of Medicine, Bar-Ilan University*

Our perception of the world around us is not entirely veridical. Instead, our brains actively generate predictions that influence what we ultimately perceive. In this talk, I will discuss the role of our beliefs and expectations in shaping perception and ensuing physiology. Building on placebo and psychosomatic research, I will present our framework of beliefs as higher-order predictions (HOP) and discuss how beliefs shape the way we process information. Next, applying the HOP framework to physical symptoms, I will discuss recent findings regarding health beliefs and their relation to the emergence of unexplained physical symptoms. To conclude, our research aims to elucidate how our beliefs shape the reality we experience in various aspects, from information processing to well-being. A better understanding of the role of beliefs in shaping daily experiences is imperative to a better characterization of the link between mind, brain and body and may contribute to harnessing these effects to improve well-being.

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Organization of temporal patterns of behavior across a full developmental trajectory

Lior Laufer, Sharon Inberg, Shay Stern *Faculty of Biology, Technion*

During their development, animals undergo dramatic changes in their morphology, physiology and behavior. Behavioral changes are robustly organized in time, characterizing each developmental stage with specific behavioral patterns. While neuronal processes that generate temporal patterns at short timescales were identified in many species, the organization of long-term behavioral structures across the complete developmental trajectory is poorly understood. By monitoring the full behavioral trajectories of C. elegans individuals across and within all developmental stages, we discovered that a circuit of six neurons which is known to be involved in mechano-sensation is also involved in the long-term organization of behavior. The cell-death of these neurons results in new developmental structures of behavior, by either impairment of synchronization between individuals, or by the generation of alternative synchronized patterns. These different effects may result from the timing of cell death, as the behavioral desynchronization occurs when these neurons die earlier in development. According to this view, we suggest understanding the long-term behavioral patterning as a continuous dynamic process which depends on the “neuronal landscape” of the animal and may take different trajectories in this landscape. By using whole-brain imaging and circuit manipulation across different developmental stages, we aim to reveal this landscape formation.

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SLOW MATURATION OF OLFACTORY CIRCUITS UNDERLYING INNATE ODOR PREFERENCE

Elham Taha and Adi Mizrahi *The Edmond and Lily Safra Center for Brain Sciences (ELSC), The Hebrew University of Jerusalem*

In mammals, odor information is transmitted from olfactory sensory neurons to mitral cells (MCs) in the olfactory bulb. In turn, MCs transmit information to brain areas downstream, which are then read and executed as distinct behavioral output. It is still unclear whether innate and learned odor information are processed by distinct pathways. One common framework is that innate olfactory output is tunneled by MCs through the cortical amygdala (CoA), while learned olfactory output is tunneled through the piriform cortex (PC). Our aim is to reveal how the two circuits develop as the animals mature. Towards that end, we performed behavioral and anatomical experiments. Behaviorally, juvenile mice showed immature innate odor behavior as compared to adult mice. This behavioral data had a strong anatomical substrate. Specifically, using retrograde and anterograde labelling of MCs, we found that the MC-to-PC population is larger and non-overlapping with the MC-to-CoA population. Critically, the two circuits show distinct properties in juvenile mice. Taken together, these data indicate that odor circuits of innate information mature late during postnatal development, while learning related circuits are intact early on. Currently, we are using two-photon calcium imaging to assess how these distinct circuits encode learned and innate odor information.

Session C1

Chair: Tawfeeq Shekh-Ahmad

Recent Advances in Gene Therapy for Neurological Disorders

CNS-targeted Antioxidant Gene Therapy for Treating Epilepsy

Tawfeeq Shekh-Ahmad, *Department of Pharmaceutics, The Hebrew University of Jerusalem*
Aseel Saadi, Department of Pharmaceutics, The Hebrew University of Jerusalem Prince Kumar, Department of Pharmaceutics, The Hebrew University of Jerusalem Maya Sherman, Edmond and Lily Safra Center for Brain Sciences, Hebrew University of Jerusalem Albert Snowball, Queen Square Institute of Neurology, UCL, Andries Lieb, Institute of Pharmacology, Medical University Innsbruck

Epilepsy affects 1% of the global population, significantly burdens patients and society. Although many epilepsies are acquired following brain injury, available treatments only alleviate symptoms, and no effective prophylaxis or cure exists. Accumulating evidence suggests that oxidative stress plays a critical role in the development of seizures. However, non-specific antioxidant therapies may disrupt the physiological balance of oxidants/antioxidants, highlighting the need for targeted interventions. Here, we used AAV vectors to drive the expression of the Nrf2-encoding gene, which promotes the endogenous antioxidant systems, under the control of CaMKIIa, a constitutive, cell-type-specific promoter for targeting excitatory neurons. We demonstrated that our AAV-CaMKIIa-Nrf2 vectors were selectively expressed in neurons, and significantly decreased neuronal cell death in the hippocampus induced by kainic acid-SE. When injected prior to KA-SE, our AAV-CaMKIIa-Nrf2 vector dramatically reduced seizure frequency over 12 weeks and significantly decreased the total number of seizures compared to control rats. Additionally, 50% of animals remained seizure-free for 12 weeks after SE induction. Our cell type-specific approach for targeted delivery of antioxidant therapies offers a promising strategy for combating oxidative stress following brain injury, preventing or modifying the development of epilepsy, while preserving the critical balance of oxidants/antioxidants in non-affected cells.

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Dravet syndrome mouse models for novel gene therapy development

Moran Rubinstein, *Tel Aviv University*
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Preclinical models for developmental epilepsies are a vital research tool. Utilizing mouse models for Dravet syndrome (Dravet), GRIN2D, and CHD2-related developmental epilepsies, we aim to uncover the pathophysiological disease mechanism as well as develop and test the potential therapeutic efficacy of novel treatment options. Dravet, a severe developmental epilepsy with a high risk for premature death, is caused by loss of function mutations in the SCN1A gene, encoding for the voltage-gated sodium channels NaV1.1. Neuronal studies of these disease-recapitulating models demonstrated reduced excitability of inhibitory neurons and global complex synaptic changes. Recently, we developed a canine adenovirus type 2 (CAV)-mediated gene transfer of the SCN1A gene. This gene therapy significantly ameliorated Dravet phenotypes in mice, following bilateral vector injections into the hippocampus or thalamus post-seizure onset. Specifically, CAV-SCN1A improved the mice survival, reduced the occurrence of epileptic spikes and spontaneous seizures, protected from heat-induced seizures, and improved their hampered cognitive function, providing a proof-of-concept of this potential therapeutic approach for Dravet epileptic and non-epileptic comorbidities.

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Neuron-Specific AAV-Mediated WWOX Gene Therapy Rescues Mortality and Seizure Phenotypes in WOREE Syndrome Models

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Gene products of common fragile sites (CFSs), such as WW domain-containing oxidoreductase (WWOX), are well-documented in cancer and increasingly linked to neurological diseases, including epilepsy, multiple sclerosis, and Alzheimer's disease. Pathogenic bi-allelic germline WWOX variants are associated with rare autosomal recessive disorders, including spinocerebellar ataxia 12 (SCAR12) and WWOX related epileptic encephalopathy (WOREE syndrome). These disorders are characterized by severe epilepsy, profound developmental delay, and early lethality. The underlying mechanisms of WWOX actions in these disorders are poorly understood. Using genetically engineered mouse models, we demonstrated that neuronal Wwox ablation leads to brain hyperexcitability, intractable epilepsy, ataxia, profound hypomyelination, and postnatal lethality. Based on this knowledge, we next aimed to check whether neuronal WWOX delivery could rescue the phenotypes of Wwox null mice. To this end, we developed and tested an adeno-associated viral vector (AAV9) harboring human WWOX cDNA under the neuronal Synapsin I promoter (AAV9-SynI-WWOX). Testing the efficacy of optimal AAV-SynI-WWOX delivery in Wwox-null mice demonstrated that specific neuronal restoration of WWOX expression rescued brain hyperexcitability and seizures, hypoglycemia, myelination deficits, and the premature lethality and behavioral deficits of Wwox-null mice. Refinements to the vector design, including removal of the WPRE element to mitigate overexpression risks, further enhanced safety and efficacy. These findings underscore the therapeutic potential of WWOX gene therapy, paving the way for transformative treatments for devastating WWOX-associated disorders such as WOREE syndrome and SCAR12

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Neuron-Specific AAV-Mediated WWOX Gene Therapy Rescues Mortality and Seizure Phenotypes in WOREE Syndrome Models

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WWOX-related epileptic encephalopathy (WOREE) syndrome is caused by human germline biallelic mutations in WW domain-containing oxidoreductase (WWOX). WOREE is a neurodevelopmental disorder characterized by intractable epilepsy, severe developmental delay, ataxia and premature death. Using mouse genetics and patient-derived iPSCs and brain organoids, we studied role of WWOX in WOREE/SCAR12 syndromes. WWOX restoration was achieved using an adeno-associated viral vector (AAV9) harboring human WWOX cDNA and driven by the human neuronal Synapsin I promoter (AAV9-SynI-WWOX). We demonstrated that specific neuronal deletion of murine Wwox produces phenotypes typical of the Wwox-null mutation leading to intractable epilepsy, ataxia and postnatal lethality. The phenotypes of this mouse model closely resembled that of WOREE patients. In-depth characterization of these mice revealed a major myelination defect. Brain hyperexcitability as well as dramatic cellular and molecular CNS abnormalities, including neural population changes and cortical differentiation malfunctions were also revealed in human unpatterned brain organoids derived from CRISPR-engineered human ES cells and from patient-derived iPSCs. Remarkably, intracerebroventricular injection of AAV9-SynI-WWOX resulted in widespread expression of WWOX and rescued Wwox null phenotypes, including seizures, myelination defects and mortality. Our results support the clinical development of AAV9-SynI-WWOX as an effective and targeted disease-modifying approach to WOREE and SCAR12 syndromes.

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Session C3

Chair: Tal Burstyn-Cohen

Cellular interactions guiding neural development and function

developing nervous system

Mechanics of hair cell regeneration in the inner ear

Shahar Inbar Kasirer, *Tel Aviv University*
Olga Loza, Tel Aviv University David Sprinzak, Tel Aviv University

The vestibular system oversees keeping our balance by sensing acceleration and gravitation. Each of its five sensory organs consists of an alternating pattern of sensory hair cells (HCs) and non-sensory supporting cells (SCs). Mammals, in contrast to non-mammalian species, lose the capability to regenerate HCs during early development, however it is unclear why this capability is lost. Here, we use live imaging of mouse vestibular explants from transgenic mice, to track the dynamics of HC differentiation and regeneration of HCs. We track the local regeneration dynamics following laser ablation of single HCs. Our live imaging results of E17.5 and P0 utricle explain that SCs exhibit frequent cell divisions, delaminations, and differentiation events. Quantitative analysis reveals local correlations between these events and local factors such as cell morphology and neighbor types. Upon ablating a HC, we observe differentiations of nearby SCs. Comparison between explants from E17.5 and P0 reveal surprising differences in the identity of the differentiating cells. Comparison of these results with lateral inhibition models suggest that Inhomogeneous sensitivity to Notch signaling can explain the observed differences.

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Neuronal interactions with nano-based platforms for directing neuronal growth engineering

Orit Shefi, 1,3
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The ability to manipulate and direct neuronal growth has great implications in basic science and tissue engineering. Physical mechanical forces, contact guidance cues and chemical cues play key roles in neuronal morphogenesis and network formation. In this talk I will present our recent studies of 2D and 3D nanostructured scaffolds as platforms for controlling neuronal growth. We grow neurons on substrates patterned with nanotopographic cues of different shapes and materials and study the effects on neuronal geometry, dynamics and function. We compare neurons interfacing the nano-patterned substrates to neurons interfacing other neurons demonstrating a different dynamic in growth, thus, developing mechanisms translating interactions into neuronal growth behavior. In-vivo, neurons grow in a 3-dimensional (3D) extracellular matrix (ECM). Imitating the 3D environment resembling the in-vivo conditions is important for effective regeneration post trauma. We have chosen a collagen hydrogel system as the 3D ECM analog to best mimic the natural environment and develop methods to orient the collagen fibers and use them as leading cues for neurons. Current efforts to implant these modified gels to bridge gaps in injured neuronal models will be presented.

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Neural plate progenitors give rise to both anterior and posterior pituitary cells

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Qiyu Chen, Weizmann Institute of Science
Dena Leshkowitz, Weizmann Institute of Science
Hanjie, Li Weizmann Institute of Science Israel Andreas, van Impel, WWU Münster Münster Germany, Stefan Schulte-Merker, WWU Münster Münster Germany
Ido Amit, Weizmann Institute of Science
Karine Rizzoti, The Francis Crick Institute London UK

The pituitary is the master neuroendocrine gland, which regulates body homeostasis. It consists of the anterior pituitary/adenohypophysis (AH), which harbors hormones producing cells and the posterior pituitary/neurohypophysis (NH), which relays the direct passage of hormones from the brain to the periphery. It is widely accepted that the AH originates from the oral ectoderm (Rathke's pouch) whereas the neural ectoderm contributes to the NH. Using single cell transcriptomics of the zebrafish pituitary we characterized cyp26b1-positive pituicyte of the NH and prop1-positive adenohypophyseal progenitors. We found that these cell types expressed common markers implying lineage relatedness. Genetic tracing revealed that in contrast to the prevailing dogma, neural plate precursors of zebrafish (her4.3+) and mouse (Sox1+) contribute to both neurohypophyseal and adenohypophyseal cells. We further show that pituicytes and prop1+ progenitors reside in close anatomical proximity and pituicyte-derived RA-degrading enzyme Cyp26b1 fine-tunes differentiation of prop1+ progenitors into hormone-producing cells. These results challenge the notion that AH cells are exclusively derived from non-neural ectoderms and demonstrate that cross-talk between neuro- and adeno- hypophyseal cells fine-tunes the development of pituitary neuroendocrine cells.

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PROTEIN S (PROS1) REGULATES MICROGLIAL DEVELOPMENT AND FUNCTION

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Arielle Hochberg, Institute for Biomedical and Oral Research (IBOR), Faculty of Dental Medicine, The Hebrew University, Jerusalem
Katya Zelentsova-Levitskyi, Institute for Biomedical and Oral Research (IBOR), Faculty of Dental Medicine, The Hebrew University, Jerusalem
Tal Burstyn-Cohen, Institute for Biomedical and Oral Research (IBOR), Faculty of Dental Medicine, The Hebrew University, Jerusalem

Objectives: Protein S (PROS1) is a ligand to the TAM (TYRO3, AXL and MERTK) family of tyrosine kinase receptors, which are important homeostasis regulators in the brain and other systems. In the Central Nervous System (CNS), PROS1 is secreted by most cells, including neurons, astrocytes and microglia. Our goal is to understand the role of PROS1 expressed by microglia, the CNS professional phagocytes.

Methods: To investigate its importance at the neuro-immune interface, we genetically ablated Pros1 expression in the myeloid lineage, including microglia, creating Pros1-cKO mice.

Results: Pros1-cKO mice show reduced microglia numbers in adult brains, due to disturbed proliferation and apoptotic developmental waves. Moreover, microglial PROS1 shapes adult neurogenesis by negatively regulating neural stem cell proliferation and generation of new neurons. Pros1-cKO microglia show altered (activated) morphology, under naïve and inflamed conditions, and Pros1-cKO brains are more inflamed at the whole tissue level. Finally, Pros1-cKO microglia are defective in phagocytosis both in-vivo and in-vitro.

Conclusions: Our results show that microglial-derived PROS1 is necessary for normal microglial development, regulates adult neurogenesis, and underlies key anti-inflammatory mechanisms.

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Hindbrain boundaries-niches of neural progenitor/stem cells regulated by their extracellular matrix

Dalit Sela-Donenfeld, *School of Veterinary Medicine, Faculty of Agriculture, Food and Environmental Sciences, The Hebrew University*

The interplay between neural progenitor/stem cells (NPSC) and their extracellular matrix (ECM) is crucial for determining their stem/differentiation state. However, the exact mechanism of how the ECM regulates these intracellular processes remains unclear. The amniotic hindbrain is valuable to investigate this relationship, as cells at the boundaries between any two rhombomeres express the NPSC-marker Sox2 and are surrounded by the ECM proteoglycan chondroitin sulphate (CSPG). Isolating boundary cells for RNA-sequencing revealed their distinct molecular properties as typical NPSCs, expressing known and new genes related to stem cells, cancer, matrisome and cell-cycle, as opposed to rhombomere cells that exhibited a marked neural-differentiation transcriptome. By eliminating CSPG, we found that the stemness properties of boundary cells were switched to a neural differentiation state, both in-vivo and in-vitro. These findings highlight the significance of hindbrain boundaries as repetitive pools of NPSCs reliant on their microenvironment to maintain an undifferentiated neuronal state during development.

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Session C4

Chair: Boaz Barak

Myelin and oligodendrocytes in dysfunction neuropathology

White matter abnormalities in a mouse model for autism with a human-based mutation in shank3 gene

Inbar Fischer, *The Sagol School of Neuroscience, Tel Aviv University*
Sophie Shohat2,3, Yael Leichtmann-Bardoogo4, Ritu Nayak5, Gal Wiener1, Idan Rosh5, Aviram Shemen5, Utkarsh Tripathi5, May Rokach1, Ela Bar2,3, Yara Hussein5, Ana Carolina Castro6, Gal Chen7,8, Adi Soffer4, Sari Schokoroy-Trangle2, Galit Elad-Sfadia2, Yaniv Assaf1,3,9, Avi Schroeder7,Patricia Monteiro6, Shani Stern5*, Ben M. Maoz1,4,10,11*, Boaz Barak1,2,3*# 1 *The Sagol School of Neuroscience, Tel Aviv University,* 2 The School of Psychological Sciences, Faculty of Social Sciences, Tel Aviv University, Tel Aviv, Israel 3 The School of Neurobiology, Biochemistry & Biophysics, Faculty of Life Sciences, Tel Aviv University, 4 Department of Biomedical Engineering, Faculty of Engineering, Tel Aviv University, 5 Sagol Department of Neurobiology, Faculty of Natural Sciences, University of Haifa, Haifa, Israel 6 Department of Biomedicine - Experimental Biology Unit, Faculty of Medicine of the University of Porto (FMUP), Porto, Portugal 7 The Louis Family Laboratory for Targeted Drug Delivery and Personalized Medicine Technologies, Department of Chemical Engineering, Technion, Haifa, Israel 8 The Interdisciplinary Program for Biotechnology, Technion, Haifa, Israel 9 The Strauss center for neuroimaging, Tel Aviv University, Tel Aviv, Israel 10 The Center for Nanoscience and Nanotechnology, Tel Aviv University, Tel Aviv, Israel 11 Sagol Center for Regenerative Medicine, Tel Aviv University

Autism spectrum disorder (ASD) encompasses a group of developmental disorders often linked to genetic mutations, though the biological processes resulting from these mutations are not yet fully understood. The SHANK3 gene is considered a high-risk gene for monogenic ASD, as mutations in SHANK3 are found in approximately 1% of ASD patients. This gene encodes a protein that is essential for neuronal synaptic transmission, linking post-synaptic glutamate receptors to the cytoskeleton, and has been well-studied in neurons. However, its potential involvement in other critical brain functions, particularly in oligodendrocytes (OLs), remains largely unexplored. Given the essential function of OLs in producing myelin for proper brain development and neuronal function, studying SHANK3 in these cells could provide key insights into ASD pathology. Using an ASD mouse model with the InsG3680 Shank3 mutation, also expressed in humans, we revealed a previously unknown role for Shank3 in post-synaptic

OL features, similar to its role in neurons. We found that Shank3-mutated primary OL cultures exhibit impaired molecular and physiological glutamatergic traits. In vivo, Shank3-mutated mice showed significant reductions in the expression of key myelination-related transcripts and proteins, along with deficits in myelin ultrastructure, white matter, axonal conductivity, and motor skills. Finally, we observed clinically relevant impairments in induced pluripotent stem cell-derived OLs from a patient with the InsG3680 mutation. Together, our study provides insight into Shank3's role in OLs and reveals a mechanism linking myelination to ASD pathology. This opens new avenues for targeted, effective treatments for SHANK3-related ASD.

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Oligodendrocyte aging and rejuvenation

Tal Iram, *Stanford University, CA, USA*
Fabian Kern, Saarland University Saarbrücken, Germany Achint, Kaur Stanford University, CA, USA, Henrik Zetterberg, Sahlgrenska University Hospital, Mölndal, Sweden Andreas Keller, Saarland University Saarbrücken, Germany J Bradley Zuchero, Stanford University, CA, USA Tony, Wyss-Coray, Stanford University, CA, USA

Recent understanding of how the systemic environment shapes the brain throughout life has led to numerous intervention strategies to slow brain aging. Cerebrospinal fluid (CSF) makes up the immediate environment of brain cells, providing them with nourishing compounds. We discovered that infusing young CSF directly into aged brains improves memory function. Unbiased transcriptome analysis of the hippocampus identified oligodendrocytes to be most responsive to this rejuvenated CSF environment. We further showed that young CSF boosts oligodendrocyte progenitor cell (OPC) proliferation and differentiation in the aged hippocampus and in primary OPC cultures. We identified serum response factor (SRF), a transcription factor that drives actin cytoskeleton rearrangement, as a mediator of OPC proliferation following exposure to young CSF. With age, SRF expression decreases in hippocampal OPCs, and the pathway is induced by acute injection with young CSF. We screened for potential SRF activators in CSF and found that fibroblast growth factor 17 (Fgf17) infusion is sufficient to induce OPC proliferation and long-term memory consolidation in aged mice while Fgf17 blockade impairs cognition in young mice. These findings demonstrate the rejuvenating power of young CSF and identify Fgf17 as a key target to restore oligodendrocyte function in the aging brain.

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The journey to cell therapy for demyelinating diseases

Tamir Ben-Hur, *MD PhD Department of Neurology, Hadassah – Hebrew University Medical Center*

Multiple sclerosis (MS) is an immune mediated demyelinating disease of the central nervous system, and a major cause of non-traumatic neurological disability in the young adult population. Myelin regeneration is a major therapeutic target, to improve functional injury, and to protect axons from irreversible degeneration. Re-myelination can be achieved either via promoting (the failing) endogenous repair processes or by introducing cell therapy. Our early studies in neural stem/precursor cell therapy identified previously unknown immune-modulatory, neurotrophic and neuroprotective properties of these cells. These findings suggested a major role of adult tissue progenitor cells in protecting their microenvironment, rather than "sitting and waiting" for injury and repair. Indeed, we could show an acquired failure in these properties in resident neural precursor cells derived from a model of neurodegenerative disease. While these findings were translated into clinical trials using the immune-modulatory and neurotrophic properties of non-neural precursors (such as mesenchymal stem cells) in MS and ALS, the challenge of re-myelinating cell therapy has not been met yet. To that end, we have developed a human embryonic stem cell (hESC) platform and studied it in a clinical relevant mouse model of progressive multiple sclerosis. We found that early human progenitors of the oligodendroglial lineage exert persistent immune-modulatory effects in the chronic MS model, but were not effective for re-myelination. Transplanting hESC -derived late oligodendrocyte progenitors, resulted in highly effective migration and differentiation of the cells into mature oligodendrocytes and increase in myelin content. These findings may open for the first time the potential of regenerative cell therapy in demyelinating diseases.

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Session C5

Chair: Gali Umschweif Nevo

cellular and molecular regulation of stress-induced behavior

Neurensin-2: a novel cell-type-specific stress-responsive protein

Gali Umschweif-Nevo, *the Hebrew University*

Emotional stress is a major risk factor for anxiety and depressive disorders. In both human disease and rodent models of anxiety and depression, hippocampal excitation/inhibition (E/I) imbalance is evident, implicating this imbalance in stress-related behaviors. Indeed, hippocampal inhibitory interneurons that dictate E/I balance are critical players in depression and anxiety disorders. However, the molecular adaptations of inhibitory interneurons to emotional stress are poorly understood. Recently, we identified a novel stress-responsive protein, namely, Neurensin-2. Neurensin-2 is expressed selectively in subtypes of hippocampal interneurons, including the CCK cells, and is massively upregulated after chronic stress. This vesicular protein directly and bidirectionally regulates the excitatory inputs onto the inhibitory neurons. Furthermore, Neurensin-2 in CCK cells induces anxiety and depression-like behaviors, while deletion of Neurensin-2 results in stress resilience. To identify the molecular role of Neurensin-2, we used an in-vitro stress model and Neurensin-2 overexpression followed by RNA-seq. Our results suggest that Neurensin-2 regulates E/I balance by modulating the expression of the CB1 receptor in CCK cells. These data suggest novel cell-type-specific molecular adaptations to stress that underlie hippocampal E/I shift and consequent behavioral deficits. Furthermore, these findings implicate Neurensin-2 in the pathophysiology and future treatments of stress-related disorders, such as depression and anxiety.

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THE DORSAL DENTATE GYRUS – A SURPRISING PLAYER IN STRESS VULNERABILITY AND RESILIENCE

Gal Richter-Levin, *Sagol Department of Neurobiology, University of Haifa*

In earlier studies of the hippocampus, the focus was the CA areas, with their impressive "Place Cells", and the dentate gyrus was referred to as a gate for cortical information into the hippocampus proper. This view changed over the years, but the later developed concept of "dorsal hippocampus – cognitive; ventral hippocampus – emotional", left little room for assuming any emotion-related role for the dorsal dentate gyrus (dDG). In contrast to that, accumulating findings we obtained suggested that the dDG holds an important role in defining the outcome of exposure to a stressful experience. The development of the "Behavioral Profiling" analysis approach, which enables differentiating between Exposed-Affected and Exposed-behaviorally-Unaffected individuals, opened the way to examine the role of the dDG in stress vulnerability and resilience. Post-trauma alterations within the dDG, selectively associated with Behaviorally Affected or Behaviorally Unaffected individuals, further supported the notion that the dDG is an important player in defining the outcome of trauma-exposure. Selective, intra-dDG manipulations of expression of specific target proteins further support that view. Taken together, our findings indicate that, far more than was envisaged before, the dDG is an important player in defining the outcome of stressful or traumatic experiences.

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Serotonergic regulation of peripheral immune cell recruitment to the brain

Dorit Farfara
Peter Androvic, Katrin Perez Anderson, Margarita Sirotkin, Hilla Azulay-Debby, Ozgun Gokce, Asya Rolls, *Technion*

Peripheral immune cells play a critical role in brain activity, but the mechanisms regulating their recruitment to the brain (and its borders) remain largely unknown. Here, we demonstrate in mice that serotonin regulates the infiltration of peripheral immune cells to the brain compartment. Chemo genetic activation of dorsal raphe serotonergic neurons increased the abundance of peripheral immune cells in the brain. These effects were mediated via the 5-HT2C receptor, which we localized to the choroid plexus using spatial transcriptomics. Through pharmacological manipulation of this receptor, we confirmed its essential role in the recruitment process. Mechanistically, 5-HT2C receptor activation induced a localized increase in the chemokine SDF-1, further demonstrating its role by blocking its receptor, CXCR4. Finally, we show that Selective Serotonin Reuptake Inhibitors (SSRIs), known to increase serotonin levels, also promote peripheral immune cell infiltration to the brain. Blocking the 5-HT2C/SDF-1 axis in SSRI-treated mice prevented this immune cell entry and abolished the therapeutic effects of SSRIs. Collectively, these findings identify serotonin as a "gatekeeper" for the brain's immune composition, with implications for the treatment of autoimmune disorders, neurodegeneration, stress and depression.

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A paradigm shift in translational psychiatry through rodent neuroethology

Yair Shemesh, *Weizmann Institute of Science*

Rodents as animal models of stress-related psychopathology are essential for preclinical investigations of conserved mechanisms of action and candidate therapeutic agents. However, highly controlled tests in impoverished environments and social contexts as proxies for complex human behavioral disorders might have limited face validity. Conversely, animal models that are monitored in more naturalistic environments over long periods display complex and ethologically relevant behaviors that reflect evolutionarily conserved endophenotypes of translational value. In our semi-natural setup (the social box), groups of mice are individually tagged and video recorded continuously. We use open-source machine-learning techniques for pose estimation that enable continuous and automatic tracking of individual body parts in groups of rodents over long periods. The trajectory of each animal is subjected to supervised machine-learning algorithms for an automatic detection of specific behaviors. We incorporated pharmacology, optogenetics, and chemo genetics in the social box to manipulate the CRF stress system and oxytocinergic system and study their role in regulating complex group interactions. I will present our findings and discuss how an ethologically oriented approach can complement classical behaviorism.

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Biophysical mechanism underlying epigenetically inherited stressful behavior

Alaa saleh- phD student

Edi barkai-P. I

Inna Gaisler Salomon-P. I

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Stressful behavior has been shown to be transferred epigenetically. Here we study the biophysical mechanism of such epigenetic inheritance. Mice were exposed to varying protocols of tone-shock fear conditioning: a predictable group exposed to repetitions of consistent pairs of tone-shock; an unpredictable group exposed to tone and shocks in a random order. After two weeks, all groups were exposed to the tone only for three days. The unpredictable group exhibited significantly higher freezing than both naive and predictable groups on all three days. This enhanced response was accompanied by reduced post-burst after-hyperpolarization (AHP) amplitude in pyramidal neurons of the anterior insula. Subjects of the three groups were paired for breeding, and first-generation offspring were exposed to one tone-mild shock pair followed by three days of tone-alone exposure. Offspring of both predictable and unpredictable subjects exhibited significantly higher freezing levels than offspring of naïve parents, with significantly higher responsiveness in offspring of the unpredictable group. Additionally, offspring of the unpredictable group were born with lower AHP amplitude in the anterior insula neurons. These results indicate that experiencing unpredictable stress can alter the neuronal properties of the insula's neurons and the behavioral response to fear.

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Session C6

Chair: Bruce Hope

Molecular, cellular, and circuit mechanisms of drug-related learning

PROBING THE CIRCUIT UNDERLYING COCAINE-INDUCED STEREOTYPIES WITH A NOVEL BEHAVIOR ANALYSIS PLATFORM

Itay Shalom, *Edmond & Lily Safra center for Brain Sciences, The Hebrew University of Jerusalem*
Ben Jerry Gonzales, Edmond & Lily Safra center for Brain Sciences, The Hebrew University of Jerusalem
Ami Citri, Edmond & Lily Safra center for Brain Sciences, The Hebrew University of Jerusalem, Program in Child and Brain Development, Canadian Institute for Advanced Research, MaRS Centre, Canada

Neuroethology emphasizes the need to quantify the association of neural activity with animal behavior, with a focus on naturalistic behaviors. However, quantifying the behavior of freely moving animals is technologically challenging. In this talk, I will present STEREO, an advanced annotation system I am developing, which offers a detailed description of freely moving mice behavior from raw video feeds. STEREO implements a CNN-LSTM architecture, leveraging spatiotemporal information from video snippets to classify single-frames to behavioral categories. By applying STEREO to video recordings of mice repeatedly exposed to cocaine, we were able to quantify nuanced cocaine-induced orofacial behaviors, revealing a striking gradual narrowing of the behavioral repertoire over time. To further investigate the underlying circuitry governing motor execution, we used STEREO to align the dynamics of Drd1+- vs A2A+- ventrolateral striatal (VLS) spiny projection neurons (SPNs) Ca2+ activity to behavior. Doing so, we observed a differential activity pattern of the two striatal projection populations with respect to the performed behavior. Finally, we used STEREO to quantify the changes induced in the landscape of behavior following optogenetic and chemogenetic modulation of VLS dSPN and iSPN activity, illustrating the causal relationship between the activity of these cells and the motor execution of orofacial/upper-limb actions.

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Cell types and unique transcriptomic alterations of neuronal ensembles activated by cocaine-induced

Bruce T. Hope,
Katherine E. Savell, Rajtarun Madangopal Affiliation: *Neural Ensembles in Addiction Section, BNRB, NIDA IRP, NIH, DHHS*

Learned associations between drug reward and related cues are encoded within specific patterns of sparsely distributed neurons, called neuronal ensembles. We and others have identified ensembles encoding many different behaviors. However, very few studies identified molecular and cellular alterations in ensembles that allow them to store these learned associations. We used transgenic Fos-mRFP rats in one experiment, and the permanent fluorescent marker of increased intracellular calcium (CaMPARI) in a second experiment, to identify activated nuclei from medial prefrontal cortex (mPFC) of male and female rats following cue-induced relapse to cocaine seeking or novelty exposure. Fluorescence-activated nuclei sorting (FANS) was used to enrich for activated mRFP-labeled nuclei and activated red CaMPARI-labeled nuclei to compare with non-activated nuclei from the same samples. Single nuclei RNAseq indicated that all subtypes of glutamatergic and GABAergic cell types were activated during cocaine relapse (and novelty exposure). Nearly all gene alterations were found only in the small percentage (~5%) of activated neurons with almost no alterations in the non-activated neurons that make up most neurons. Overall, neuronal ensembles thought to encode learned associations between drug reward and related cues induce a unique transcriptomic signature in all subtypes of rat mPFC neurons following cocaine relapse.

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Role of the translational mechinary in cocaine-induced behaviours

Rami Yaka
Tehila Beiser, Elvira Lisniansky, Moriya Weitz, Alexey Bingor, Kobi Rosenblum
Hebrew University, Jerusalem

Recent evidence links synaptic plasticity and mRNA translation, via the eukaryotic elongation factor 2 kinase (eEF2K) and its only known substrate, eEF2. However, the involvement of the eEF2 pathway in cocaine-induced neuroadaptations and cocaine-induced behaviours is not known. Knock-in (KI) mice and shRNA were used globally and specifically reduce eEF2K expression. Cocaine psychomotor sensitization and conditioned place preference were used to evaluate behavioral outcome. Changes in eEF2 phosphorylation were determined by western blot analyses. No effect was observed on the AMPA/NMDA receptor current ratio in the ventral tegmental area, 24h after cocaine injection in eEF2K-KI mice compared with WT. However, the development and expression of cocaine psychomotor sensitization were decreased in KI mice. Phosphorylated eEF2 was decreased one day after psychomotor sensitization and returned to baseline at seven days in the nucleus accumbens (NAc) of WT mice, but not in eEF2K-KI mice. However, one day following the cocaine challenge, phosphorylated eEF2 decreased in WT but not KI mice. Importantly, specific targeting of eEF2K expression by shRNA in the NAc decreased cocaine condition place preference. These results suggest that the eEF2 pathway plays an important role in cocaine-induced locomotor sensitization and conditioned place preference.

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Long-term alcohol consumption enhances accumbal myelination and impairs neural connectivity

Segev Barak, *School of Psychological Sciences, the Sagol School of Neuroscience, the George Wise Faculty of Life Sciences, Tel Aviv University*
Mirit Liran, the George Wise Faculty of Life Sciences, Tel Aviv University

Background: Alcohol Use Disorder (AUD) involves loss of control over alcohol consumption and is associated with myelin-related changes in the mesocorticolimbic system, potentially contributing to addiction phenotypes. However, the specific characteristics of these myelin abnormalities remain unclear. Here, we characterized myelin-related changes, and mesocorticolimbic microstructural and connectivity modifications, following long-term voluntary alcohol consumption in mice.

Results: Long-term (12-week) voluntary alcohol consumption led to increased myelin thickness in the nucleus accumbens (NAc) and upregulated the expression of myelin-related genes, including Myrf, Mbp, Plp1, and Mag, which play a role in myelination processes, in the NAc and medial prefrontal cortex (mPFC). Long-term alcohol exposure also altered oligodendrocyte precursor cells' differentiation and maturation in a time-dependent manner. Chronic administration of clemastine, which enhances myelinating oligodendrocytes, led to increased alcohol consumption, suggesting that hypermyelination contributes to alcohol intake escalation. Finally, we conducted a longitudinal diffusion tensor imaging (DTI-MRI) analysis, revealing microstructural changes in the NAc and mPFC, as well as disrupted fiber tracts connectivity between these regions, following alcohol consumption.

Conclusions: Our results suggest that prolonged alcohol consumption leads to hypermyelination in the NAc, and alters the cortico-accumbal organization, density, and connectivity, implicating myelination dysfunction in alcohol addiction.

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Synaptic plasticity alterations in ventral pallidal circuitry after abstinence from cocaine

Yonatan Kupchik, *The Hebrew University of Jerusalem*
Liran Levi, The Hebrew University of Jerusalem

Objectives The Ventral Pallidum (VP) is a central hub of the reward system that contains a sub-population of glutamatergic neurons. We describe here how the synapses these neurons make in the lateral habenula (LHb) and the ventral tegmental area (VTA) change through the course of exposure to cocaine, withdrawal and re-exposure to cocaine after withdrawal.

Methods vGluT2-Cre mice were injected with AAV-DIO-ChR2-eGFP in the VP to express ChR2 in VP glutamatergic neurons and then went through the cocaine conditioned place preference (CPP) protocol. Mice were sacrificed at three time points – after conditioning, after withdrawal and after re-exposure to cocaine – and we recorded the VP glutamatergic input to the VTA and LHb with slice electrophysiology.

Results We found that the VP glutamatergic synapse in the LHb follows the condition of the mouse – it is weak during conditioning, strengthens after withdrawal and becomes weak again after re-exposure to cocaine. The synapse on VTA GABA neurons shows similar changes but with a different mechanism while the synapse on VTA dopamine neurons shows largely opposite changes.

Conclusions VP glutamate neurons change throughout the course of exposure and withdrawal from cocaine and thus may be important in the development of addiction.

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Session C6

Chair: Eilat students' session

Session D1

Chair: Hanna Keren

Virtual environments for the study of human behavior and perception

XR as a tool to densely study human behavior

Tom Schonberg, *School of Neurobiology, Biochemistry and Biophysics, Faculty of Life Sciences and Sagol School of Neuroscience*

Extended reality (XR) has become widely used in recent years in multiple applications from the obvious gaming industry, to education, manufacturing plants, medicine and of course in research. Here, I will show why in my view extended reality, is now one of the best tools to densely study human behavior in naturalistic environments. It allows us, not only an immersive experience, but at the same time to passively collect eye tracking, face tracking, location, and kinematics. All of these measures allow us to predict and study human behavior in settings that haven't been possible before. I will present examples from two research realms: predicting preferences and spatial navigation.

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The Neural Underpinnings of Attention and Distraction in (virtual) Realistic Environments

Elana Zion Golumbic, *Gonda Center for Brain Research, Bar Ilan University*

The ability to maintain focused attention towards a particular task or speaker and avoid distraction by irrelevant background events is crucial for many aspects of real-life behavior, including learning, memory, social communication, decision making, and self-control. However, empirical lab-based research into the cognitive and neural mechanisms underlying the constructs of 'attention' and 'distraction' has primarily focused on highly artificial paradigms, stimuli and tasks that are a far cry from the challenges of attention in real-life environments. Unfortunately, there is a growing realization that insights gained from these type of studied do not generalize well or explain behavior in real-life settings. To bridge this lab-to-real life gap, in this talk, I will present data collected using a novel VR-based experimental platform, designed for studying neural, ocular, and physiological manifestations of selective attention and distraction, under ecologically-realistic conditions that simulate those we need to deal with on a daily basis. Using two common-day scenarios, a Virtual Café and Virtual Classroom, we show how neural processing of task-relevant speech is affected by background stimuli and noise, and how the sensitivity to irrelevant stimuli varies across individuals. We also discuss implications for theories of attention and possible clinical implications for ADHD research.

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Virtual environments for the study of human behavior and perception

Roy Salomon, *University of Haifa*

Keep it Real- Using virtual reality to understand real human behaviors Neuroscience endeavors to reveal the neural processes underlying behavior and cognition. Historically this was done using paradigms which attempt to segregate behaviors into distinct processes to be studied individually. This reductionist approach has allowed to map many low-level functions of the visual and motor systems; however, it bears little resemblance to our experience in the real world. Outside the lab the world is “one great blooming, buzzing confusion” with little distinction between cognitive processes. Hence, such “controlled” experiments and their neural correlates may differ considerably from neural processing in the real world. One approach to bridge between reductionist and more naturalistic stimulations is the use of virtual reality to stimulate the real world. Here, I will outline the potentials and challenges of using VR to tackle complex and high-level cognitive phenomena such as self-consciousness and the sense of reality. These processes are inherently multisensory, and rely on online modifications of sensorimotor contingencies making them difficult to study and posing a major challenge for brain imaging. I will present examples of how virtual reality can be harnessed to allow neuroscientific investigations of complex cognitive and sensorimotor processes in well-controlled environments.

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Studying mood dynamics in a rich virtual context

Hanna Keren, *Azrieli Faculty of Medicine, Gonda Multidisciplinary Brain Research Institute, Bar-Ilan University*

Our mood has a significant impact on our functioning and metal health. It affects our cognitive, social, immunological, physiological and mental states, however, the multiple challenges involved in studying mood hinder our understanding of these relationships. The challenges include the non-linearity and variability in mood responses to the environment across individuals, strong experimental biases, and a weak impact on mood in experimental settings. I will present the Mood-Machine-Interface task, a closed-loop paradigm designed to efficiently control mood states across individuals, effectively overcoming these challenges. I will demonstrate how this task can be applied in a virtual reality setting to parametrically manipulate mood in real-time, using more complex environmental parameters. The implementation of this task in a virtual environment allows us to create multiple diverse contexts that align with or diverge from one anther. This innovative framework can thus shed light on how different environmental modalities contribute to subjective mood experiences, and moreover, it can inform the development of adaptive, individualized interfaces, for more effective and realistic influence on human mood.

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HEART RATE RELATED MEASURES RESPONSE TO VISUAL-PHYSICAL INCONGRUENT WALKING CONDITIONS

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Amit Benady, Center of Advanced Technologies in Rehabilitation, Sheba Medical Center, Israel, Orthopedic department, Tel Aviv medical center, Israel, School of Optometry and Vision Science, Faculty of Life Sciences, Bar-Ilan University, Ramat Gan, Israel.
Sharon, Gilaie-Dotan, School of Optometry and Vision Science, Faculty of Life Sciences, Bar-Ilan University, Ramat Gan, Israel, UCL Institute of Cognitive Neuroscience, London, United Kingdom, The Gonda Multidisciplinary Brain Research Center, Bar-Ilan University, Ramat-Gan, Israel.
Meir Plotnik, Center of Advanced Technologies in Rehabilitation, Sheba Medical Center, Israel, Department of Physiology and Pharmacology, Sackler Faculty of Medicine, Tel Aviv University, Israel, Sagol School of Neuroscience, Tel Aviv University, Israel.

Objectives: In recent studies using virtual reality (VR), we found specific gait modulations when visual (virtual) surface inclination was incongruent with the physical inclination. However, the extent to which such sensorimotor inconsistencies were reflected in heart rate (HR) related measures is unclear. We hypothesized that during sensorimotor incongruence HR would be higher and heart-rate-variability (HRV) would be lower (i.e., more disrupted) relative to sensorimotor congruent conditions.

Methods: In a fully immersive VR-system with self-paced treadmill that was always leveled (i.e., leveled physical inclination), healthy young adults (n=14) completed sensorimotor congruent (visual-virtual inclination leveled) or incongruent (visual-virtual inclination not leveled) walking trials while their HR was recorded. Based on congruent data, we calculated the HR to gait speed baseline relation (linear calibration) of each participant.

Results: As we anticipated, HR measures from sensorimotor incongruent periods were considerably higher than values predicted by the linear calibration, and HRV measures were significantly lower than during the congruent conditions e.g., SDNN: 62% (for downwards vision) and 65% (for upwards vision) reduction.

Conclusion: Our results show that during locomotion, HR related measures are sensitive to inconsistent sensorimotor information, simulated here as incongruent visual-physical inputs, building-up residual increase in preparation to upcoming events.

Session D2

Chair: Omer Revah

Human brain organoids in neurodevelopment and disease

MorphoNeuroChip: Unveiling Brain Malformations' Secrets at the Molecular Level

Orly Reiner, Rami Tshuva, Bidisha Bhattacharya, Tamar Sapir, Mio Nonaka
(*Weizmann Institute of Science*)
Jianping Fu, Xufeng Xue, Jeyonn Bok (University of Michigan)

The intricate development of the human neural tube remains a fundamental focus in neuroscience, with implications for understanding brain malformations and related neurodevelopmental disorders. In collaboration with the lab of Jianping Fu from the University of Michigan, we introduce the MorphoNeuroChip, a groundbreaking platform that enables the exploration of brain malformations' secrets at the molecular level. The MorphoNeuroChip leverages human pluripotent stem cells to generate patterned neural tube organoids, exhibiting precise organization along the rostral-caudal and dorsal-ventral axes. This organization is manifested through the orchestrated expression of crucial genes, including OTX2, representing the head, and genes characterizing various brain regions, such as the forebrain, midbrain, and hindbrain. Notably, the HOX genes' expression pattern along the neural tube recapitulates developmental milestones. Moreover, our continued culture of the patterned neural tube leads to the formation of critical structures like the pallium and subpallium. Single-cell RNA sequencing analysis of these patterned organoids reveals striking similarities to developing human embryos. We are harnessing the MorphoNeuroChip system to model neurodevelopmental diseases, yielding exciting and promising results. This innovative platform promises to deepen our understanding of the molecular underpinnings of brain malformations, offering potential insights into therapeutic interventions and strategies for mitigating these debilitating neurodevelopmental disorders.

A novel neuroimmune human brain organoid model to study microglia in health and disease

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Simon, Schafer , Laboratory of Genetics, The Salk Institute for Biological Studies, La Jolla, CA Johannes C.M., Schlachetzki, Department of Cellular and Molecular Medicine, University of California San Diego, La Jolla, CA, USA. Christopher K. Glass, Department of Cellular and Molecular Medicine, University of California San Diego, La Jolla, CA, USA Axel, Nimmerjahn, Waitt Advanced Biophotonics Center, The Salk Institute for Biological Studies, La Jolla, CA, USA. Fred H., Gage, Laboratory of Genetics, The Salk Institute for Biological Studies, La Jolla, CA

Microglia are specialized brain-resident macrophages that play crucial roles in brain development, homeostasis, and disease. However, until now, the ability to model interactions between the human brain environment and microglia has been severely limited. To overcome these limitations, we developed an in vivo xenotransplantation approach that allows us to study functionally mature human microglia (hMGs) that operate within a physiologically relevant, vascularized immunocompetent human brain organoid (iHBO) model. Our data show that organoid-resident hMGs gain human-specific transcriptomic signatures that closely resemble their in vivo counterparts. In vivo two-photon imaging reveals that hMGs actively engage in surveilling the human brain environment, react to local injuries, and respond to systemic inflammatory cues. Finally, we demonstrate that the transplanted iHBOs developed here offer the unprecedented opportunity to study functional human microglia phenotypes in health and disease and provide experimental evidence for a brain-environment-induced immune response in a patient-specific model of autism with macrocephaly.

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Using stem cells to build a model of the human cortex in vivo

Omer Revah, *Hebrew University, Jerusalem*

Stem cell-derived brain organoids offer new opportunities to model human brain development and disease. However, one major drawback of these tissue cultures is that they invariably fail to properly mature when maintained in vitro. This talk will focus on our recent study demonstrating that cortical organoid transplantation into newborn rats can be used to model late stages of human cortical development and identify new mechanisms of neurodevelopmental disease. Specifically, I will show that cortical excitatory neurons transplanted into the brain of newborn rats display advanced transcriptional, morphological and functional properties, which resemble those of postnatal human cells, and that advanced maturation enables discovery of disease phenotypes. Finally, I will discuss the paths forward for building an even more realistic human cortical microcircuit to be used for understanding neuropsychiatric disorders.

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Early neurodevelopment at the single-cell resolution

Miri Danan-Gotthold, *Tel Aviv University*

To achieve its cellular organization and cognitive ability, the human brain develops through precisely regulated molecular and cellular processes. Some of these processes are unique to humans and are not observed in animal models, potentially contributing to neurodevelopmental disorders that disrupt higher cognitive functions. In this study, we performed single-cell RNA sequencing of over 1.6 million cells from the human embryonic brain between postconceptional weeks 4 and 10. This detailed dataset allowed us to characterize brain development principles and delineate differentiation trajectories across various brain regions. In the neocortex, developing excitatory neuron lineages exhibited three molecular programs: differentiation from radial glia to neurons, cell cycle, and maturation. We identified two main states of intermediate progenitor cells, differentiating and proliferating, and revealed that the transition between these states occurs after the G1 phase of the cell cycle. Furthermore, developing glia displayed region-specific maturation into pre-astrocytes and oligodendrocyte precursor cells (OPCs), indicating a mechanism for adult region-specific glial types. These results highlight the significance of early patterning events and provide a valuable resource for understanding the cellular basis of human neurodevelopment and related disorders.

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Mechanomorphogenesis governed by guidance receptor Plexin-B2 is critical for gating neuronal differentiation and cytoarchitecture of neuroepithelium

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# These authors jointly supervised this work

Neuronal differentiation involves cell fate specification by instructive cues and also major physical transformation to extend neurites. The signaling pathways orchestrating the nuclear program and cytoskeletal reorganization are unclear. During development, neural tube closure is also a critical step; whether cell biomechanics of neuroprogenitors (NPCs) and differentiating neurons affects mechanomorphogenesis of the neuroepithelium is poorly understood.

Recent human genetics studies revealed rare pathogenic variants of axon guidance receptor PLXNB2 in families presenting with intellectual disability, overlapping with phenotypes seen in Plxnb2 mutant mice displaying neural tube closure defect. Here, we reveal high expression of Plexin-B2 in the germinal matrix of the human fetal brains relative to cortical regions. In hESC-derived brain organoids, Plexin-B2 is also robustly expressed in ventricular zones and cortical plates. We show that Plexin-B2 ablation severely disrupted structural integrity of ventricle-like structures, leading to smaller cerebral organoids and spatial disarray of NPCs and cortical neurons. EdU pulse-chase study also revealed premature cell cycle exit and a shrinkage of the Sox2+ NPC pool in the ventricular zone of Plexin-B2 deficient cerebral organoids

For mechanistic understanding, we compared neuronal differentiation from hESCs with or without PLXNB2 knockout, using an established neural induction protocol. Strikingly, Plexin-B2 deficient cells exhibited accelerated neuronal differentiation, forming exuberant TUJ1+ neural networks. This phenomenon was linked to a reduced actomyosin cortical layer, favoring neurite outgrowth, as well as transcriptional changes featuring cytoskeleton regulation and neurogenesis. These observations are in line with the role of Plexin-B2 in controlling actomyosin contractility and cell stiffness of hNPCs as shown in our recent study, which in turn feeds back into gene programs controlling neurogenesis. Structure-function analysis further demonstrated that Plexin-B2 signals through its Ras-GAP domain to regulate mechanomorphogenesis, while the bendable extracellular ring domain was also indispensable shown by failure of locked-ring mutants of Plexin-B2 to rescue the KO phenotype. Ongoing single-nuclei RNA sequencing analysis of Plexin-B2 KO brain organoids and of prematurely differentiated Plexin-B2 KO neurons will uncover mechano-regulatory elements underlying a primary role of Plexin-B2 in regulating cell mechanics and physical transformation during neuronal differentiation. Unraveling the mechanomorphogenetic function of Plexin-B2 during early stage of neuronal cell fate specification will help advance understanding of neurodevelopmental disorders associated with Plexin mutations and facilitate generation of induced neurons for disease modeling.

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Session D3

Chair: Pablo Blinder

New insights into Brain Barriers development and function

Unique features of the arterial Blood-Brain Barrier

Batia Bell, Shira Anzi, Esther Sasson and Ayal Ben-Zvi
Department of Developmental Biology and Cancer Research, Faculty of Medicine, Hebrew University of Jerusalem, Jerusalem

Approximately 140 years have passed since the discovery of the Blood-Brain Barrier (BBB) and 55 years since its cellular components were identified. Now, by using new imaging approaches we uncover unique features of the arterial Blood-Brain Barrier. Recent evidence suggests that there is molecular heterogeneity among the different components of the Neurovascular Unit (NVU), particularly among endothelial cells, across different types of CNS vessels. These findings, mainly obtained from single-cell mRNA sequencing profiling, have led us to investigate the possibility of cell biological and functional heterogeneity in barrier properties and to investigate barrier properties of arterial walls. Using tracer challenges and various imaging modalities, we discovered that at the mouse cortex, the arterial barrier does not reside at the classical level of the endothelium. The arterial wall's unique permeability acts bi-directionally; CSF substances travel along the glymphatic path and can penetrate from the peri-vascular space through arteriolar walls towards the lumen. We found that caveolae vesicles in arteriole endothelial and smooth-muscle cells are functional transcytosis machinery components, and that a similar mechanism is evident in the human brain. Based on our findings, we suggest shifting from a unifying view of the classical BBB to acknowledge structural and functional barrier heterogeneity.

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Nanobubble-mediated BBB opening as a platform for enhanced delivery to brain capillaries

Tali Ilovitsh, *Department of Biomedical Engineering, Tel Aviv University, Israel*

Microbubble-mediated BBB opening can facilitate drug delivery to the brain. We developed a method to assess BBB opening at a single blood vessel resolution and showed that reduced microbubble oscillations in smaller blood vessels, together with lower concentration in capillaries, limit BBB opening in small blood vessels. Here, we aim to improve BBB opening in capillaries through the use of 180 nm nanobubbles and low frequency ultrasound. Mice were injected with 180 nm nanobubble, treated with 250 kHz FUS and injected with two fluorescent dye markers: 1) 1,4,70, or 150kDa red dextran for BBB extravasation assessment. 2) FITC-labeled dextran for blood vessels labeling. An automated image processing pipeline was developed to quantify the extent of extravasation as a function of microvasculature diameter, including a wide range of vascular morphological parameters and comparison to microbubble-mediated BBB opening. For capillaries smaller than 6 µm, BBB opening was significantly enhanced with nanobubbles. Extravasation decreased with molecular weight. In summary, the smaller nanobubbles diameter can facilitate their entry into capillaries and promote a more uniform BBB opening in large and small blood vessels, thus improving brain delivery.

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Neuropeptide oxytocin facilitates its own brain-to-periphery uptake

Preethi Rajamannar, *Dept. of Molecular Neuroscience & Dept. of Molecular Cell Biology, Weizmann Institute of Science*
Oren Raz, Dept. of Physics of Complex Systems, Weizmann Institute of Science
Gil Levkowitz, Dept. of Molecular Neuroscience & Dept. of Molecular Cell Biology, Weizmann Institute of Science

The hypothalamo-neurohypophyseal system is an important neuroendocrine brain-to-blood conduit through which the neurohormones oxytocin and arginine-vasopressin are released from the brain into the general circulation to affect peripheral physiological functions such as salt balance, metabolism and reproduction. However, the mechanism, which executes fast and efficient neurohormone release to the periphery remains unsolved. We show, using live imaging in zebrafish, that a hyperosmotic physiological challenge elicits a local increase in neurohypophyseal blood flow velocities and a change in capillary diameter, which is dictated by the geometry of the hypophyseal vascular microcircuit. Genetic ablation of oxytocin neurons and inhibition of oxytocin receptor signaling attenuated changes in capillary blood flow and diameter. Optogenetic stimulation of oxytocin neurons resulted in an oxytocin receptor-dependent increase in blood flow velocities. Lastly, both osmotic challenge and oxytocin neuronal activation elicited a local rise in neurohypophyseal capillary permeability in an oxytocin signaling-dependent manner. Our study demonstrates that physiologically elicited changes in neurohypophyseal blood flow and permeability are regulated by oxytocin. We propose that oxytocin-dependent neuro-vascular coupling facilitates its efficient uptake into the blood circulation, suggesting a self-perpetuating mechanism of peripheral hormone transfer.

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Blood Brain Barrier Dysfunction in Drug Resistance Epilepsy: A Multi-Center Feasibility Study

Nir Cafri1,2
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2. Department of Neurology, Rabin Medical Center, Beilinson Hospital and Tel-Aviv University, Israel
3. Department of Medical Neuroscience, Dalhousie University, Halifax, Canada,
4. Division of Neurology, and
5. Neurosurgery, Nova Scotia Health Authorities and Dalhousie University, Halifax, Canada

Blood brain barrier dysfunction (BBBD) is a phenomenon that has been linked to various neurological disorders, including epilepsy. Dynamic contrast-enhanced MRI (DCE-MRI) is a commonly used method to assess BBBD, and several models have been proposed to quantify this phenomenon. Epilepsy is a chronic neurological disease that is characterized by spontaneous seizures, and approximately 30% of patients with epilepsy do not respond to currently available antiepileptic drugs. In this study, we sought to assess the difference in BBBD between patients with epilepsy and healthy controls using DCE-MRI using the Veksler linear and tofts analysis. We found that patients with epilepsy had significantly higher levels of BBBD compared to healthy controls especially in several specific regions. On the other hand, we observed that the BBBD levels were similar in patients with partial seizures compared to those with idiopathic generalized epilepsy. These findings suggest that BBBD may be an important factor in the development and progression of epilepsy, and that targeting BBBD may offer a potential therapeutic approach for this disease. Overall, this study provides new insights into the role of BBBD in epilepsy and highlights the potential of DCE-MRI as a tool for assessing this phenomenon in human patients.

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Exosomes from neural cells enhance barrier functions in iPSC-based model of the human BBB

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The blood-brain barrier (BBB) is a highly selective barrier that is formed as a multicellular neurovascular unit (NVU) in which pericytes, astrocytes and neurons come in direct contact with brain microvascular endothelial-like cells (BMECs). In turn, BMECs from specialized barrier properties created by tight junctions (TJs), which limit the paracellular passage of molecules. Discrepancies across species limit the use of animal models to test BBB for predicting drug delivery into the human CNS. To faithfully mimic the in vivo BBB, in vitro models must display physiologically relevant BBB properties including high levels of transendothelial electrical resistance (TEER) and low paracellular permeability. iPSC-derived BMEC (iBMEC) monolayers seeded on transwells provide a useful platform for BBB modeling. When co-cultured with neural cells, iBMECs display increased barrier properties, indicating an intracellular crosstalk. We hypothesize that this crosstalk is at least in part, mediated by exosomes.

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Session D4

Chair: Yuval Nir

Sleep: unconscious restoration, from molecules to behavior

Sleep and Repair of DNA breaks

Gali Krayden, Michal Zarfati, Julia Sharabany and Lior Appelbaum

The Faculty of Life Sciences and the Multidisciplinary Brain Research Center, Bar-Ilan University, Ramat-Gan

Sleep is vital for the survival of all animals, ranging from jellyfish to fish and humans. Sleep improves brain performance, such as memory and learning, however, even invertebrates with simple nervous system sleep, and the core cellular function of this enigmatic behavior is unclear. We propose that single neuron, located within intact networks, require sleep across evolution. We combine imaging of DNA damage response proteins, CRISPER-mediated genetic manipulations, real time imaging of neuronal activity, as well as video tracking of behavior to study the interaction between sleep, neuronal activity, DNA damage and repair. We suggest that sleep upregulates nuclear maintenance in neurons.

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Homeostatic regulation of CA1 firing rate set points and contextual memory retrieval in mice

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Homeostatic mechanisms stabilize activity of neural circuits by keeping firing rates in a given circuitry within a set-point range. Accumulated evidence suggests that mean firing rate (MFR) is found under homeostatic regulation. However, whether the hippocampus is capable of homeostatic regulation of MFR in response to a chronic perturbation is unknown. We applied long-term single-unit recordings in freely behaving mice to measure spontaneous spiking activity of CA1 pyramidal neurons under the baseline spontaneous activity and in response to chronic chemogenetic perturbation (Gq-DREADD) of hippocampal interneurons. Clozapine N-oxide (CNO) was applied via osmotic pump for five days to achieve a constant perturbation. Our results show that Activation of Gq-signaling in interneurons led to an acute suppression of MFR across a population of CA1 pyramidal cells that gradually recovers after 3 days returning to the original MFR set-point value. Interestingly, MFR returned to its brain state-specific set-point value. Additionally, mechanisms that restore MFR at the population level also restore contextual memory retrieval in fear conditioned mice. This study provides the first direct evidence on homeostatic regulation of MFR set points by brain states and points to the role of homeostatic mechanism in preserving hippocampus core function to retrieve stored memories.

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Sleep and sedation in basal ganglia in health and Parkinson's disease

Halen Baker, *Hebrew University, Jerusalem*

Sleep disorders are common and disabling symptoms of Parkinson's disease (PD). Deep brain stimulation (DBS) is a standard care procedure for patients with advanced PD. In many centers, DBS is performed with the patient awake to optimize physiological navigation to the DBS target. In this talk, I will summarize our studies of basal ganglia physiology before and after the induction of Parkinsonism by the MPTP neurotoxin. Sleep can be divided into rapid eye movement (REM, (paradoxical, dream sleep) and Non-REM (NREM) sleep. NREM sleep induces a reduction of discharge rate and bursty firing pattern in most stations of the thalamocortical – basal ganglia networks, whereas discharge rate and pattern during REM sleep resemble the discharge during the awake state. I will show that reliable physiological navigation to DBS targets can be achieved with interleaved propofol-ketamine sedation protocol that mimics the NREM-REM cycle. Finally, I will set the frame for future phase- and frequency-specific closed-loop DBS treatment of PD, which hopefully will restore normal sleep architecture and slow the progression of PD.

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Sleep and memory consolidation in health and disease

Yuval Nir 1,2,3,4
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Sleep promotes memory consolidation. In a series of studies in humans, we improving the understanding of this phenomenon by developing novel behavioral paradigms, by performing interventions during sleep, and by investigating changes in sleep and memory in early dementia. Most research on human sleep and memory uses exhaustive learning of word-pair associations. We introduce two alternatives; First, a visual paired association learning (vPAL) paradigm with associations between images of celebrities and animals; Second, an ecological 'no-report' paradigm whereby upon repeated viewing of special movies, eye gaze patterns quantify episodic memory without report. Next, we show that deep brain closed-loop intracranial electrical stimulation during human sleep enhances hippocampus-cortex synchrony and memory performance. Finally, we examine how sleep and memory decline in dementia. Alzheimer's disease (AD) patients show a wide range of sleep impairments, but in early amnestic mild cognitive impairment (aMCI), the key difference is longer REM sleep onset latency that correlates with worse overnight memory consolidation. We also developed a novel machine learning-based method to non-invasively detect interictal spikes occurring in the medial temporal lobe during sleep. This approach now allows identifying disruptions in hippocampus-cortex synchrony and memory consolidation during sleep.

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Unconsciousness Dynamics: From Sleep to Disorders of Consciousness

Anat Arzi, *Departments of Medical Neurobiology & Cognitive and Brain Science, Hebrew University of Jerusalem*

Consciousness is dynamic. Every day, it naturally fades away when we fall asleep and re-emerges when we wake up. Loss of consciousness and consciousness recovery may also occur following a severe brain injury. How does our ability to process information depend on the level of consciousness we experience? To answer this question, we exploit the unique interaction between the sense of smell, respiration, and consciousness to examine the interplay between consciousness dynamics and sensory processing. We conducted a comprehensive study involving patients with disorders of consciousness (vegetative state/unresponsive wakefulness syndrome and the minimally conscious state) during their rehabilitation. We repeatedly measured nasal airflow both at rest and in response to pleasant and unpleasant odors and found a gradual evolution of respiratory patterns during consciousness recovery, unveiling a progressive increase in variability, followed by a non-discriminatory response, and finally, culminating in a discriminatory response. Furthermore, evidence for olfactory processing can reappear weeks before gold-standard behavioral measures for consciousness detection. These findings uncover how sensory processing unfolds during the recovery of consciousness and open new avenues for tracking changes in consciousness levels, which often remain undetected by standard behavioral assessment tools.

Session D5

Chair: Ramon Birnbaum

Neuronal transcription regulation

Pluripotent stem cell models reveal altered genetic and epigenetic pathways in Huntington's disease

Moria Maman, Hebrew University
Elad Dvir, Hebrew University
Xue Sun, Hebrew University
Oren Ram, Hebrew University
Sagiv Shifman, Hebrew University
Eran Meshorer, *Hebrew University*

Huntington's disease (HD) is a genetic neurodegenerative disorder, caused by an expansion of CAG repeats (>39) coding for poly-glutamine (polyQ) tract in the Huntingtin (HTT) gene. Although HD is late onset, it was shown to have an early neurodevelopmental component. Here we sought to unveil early pre-symptomatic alterations using cerebral organoids from juvenile forms of isogenic HD pluripotent cells. Single cell RNA-seq of dissociated organoids from 72Q-iPSCs revealed accelerated neurogenesis in the HD cells. RNA-seq comparing HTT-knockout (KO) and 72Q organoids identify several altered pathways, of which premature neuronal differentiation was shared between the KO and HD systems, supporting a loss-of-function origin. To identify mutant HTT-specific interacting proteins, we endogenously labelled both WT and mutant HTT alleles in 72Q-iPSCs and performed pulldown experiments followed by mass spectrometry (LC-MS/MS) in iPSC-derived organoids. Among the exclusive interactors with mutant HTT was DNMT3B. Accordingly, we found wide-spread DNA de-methylation in the mutant cells (72Q and 180Q), which also displayed increased predicted epigenetic age, and was more pronounced in 180Q organoids. Taken together, our findings reveal fundamental neurodevelopmental and epigenetic defects in the early stages of neurogenesis in HD models, highlighting DNA methylation as a central pathway in early HD.

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Forebrain neuronal Smc3 regulates appetite, weight, and metabolic heath

Natalia Saleev, Bar Ilan University Faculty of Medicine Dmitriy Getselter, Bar Ilan University Faculty of Medicine
Evan Elliott, *Bar Ilan University Faculty of Medicine*

SMC3 is a major component of cohesin complex that regulates higher-order chromatin organization and gene expression. Mutations in SMC3 gene are found in patients with Cornelia de Lange syndrome (CdLs). This syndrome is characterized by intellectual disabilities, behavioral patterns such as self-injury, as well as metabolic dysregulation. Nonetheless, little is known about the exact role of SMC3 in neuronal maintenance and gene expression, especially in adulthood. This study determined the role of SMC3 in adulthood brain, by knocking out Smc3 specifically in adulthood excitatory neurons. Neuron-specific SMC3 knockout mice displayed dysregulated a very strong metabolic phenotype in both male and female mice, including a robust overweight phenotype, loss of muscle mass, differences of respiratory exchange, heat production and hormonal changes. The hypothalamus of these mice displayed dysregulated morphology and RNA-seq in the hypothalamus reveals dysregulation in multiple cellular pathways, including decrease of Melanocortin 4 receptor (Mc4r), a main regulator of appetite. Treatment of these mice with Setmelanotide, a MC4r agonist, induced a decrease of weight and food consumption in these mice. Therefore, we have identified specific metabolic pathways that are regulated by Smc3 in forebrain neurons, and specific mechanisms that are involved. These may inform clinical treatment of individuals with CdLs.

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Probing and Reprogramming Transcriptionally Active Liquid Bodies in Living Cells

Dan Bracha, *Faculty of Biotechnology and Food Engineering, Technion*

Cells compartmentalize biomolecules of shared function to coordinate complex cellular tasks. Condensation of biomolecules represents a membrane-free compartmentalization strategy that relies on the remarkable ability of specialized proteins to phase-separate into liquid-like bodies. These include many nuclear bodies, such as Nucleoli, Nuclear speckles, and Cajal bodies, where transcriptional activity drives and regulates phase separation. Phase-separating proteins are predominantly unstructured and are implicated in the pathology of many neurodegenerative disorders due to their enhanced aggregation propensity. However, the driving forces underlying the biogenesis of disordered protein assemblies and the collective modes of function that regulate their structure and biochemistry are poorly understood. Studying these dynamic structures and elucidating the link between their physicochemical nature, function, and dysfunction pose a major challenge for conventional molecular biology and biophysical technologies. In this talk, I will present a controllable bioengineering approach for manipulating the intracellular phase behavior of condensates, reprogramming their spatial distribution and material properties, and quantitatively studying their biochemical properties. These technologies have enabled us to map protein-specific phase-diagrams in live cells, providing quantitative insights into the driving forces underlying the assembly and disassembly of membranelles organelles and the causality between phase-separation propensity and the onset of pathological aggregation.

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Regulation of neuronal chromatin environments by long noncoding RNAs

Igor Ulitsky, *Weizmann Institute of Science*

Intergenic regions in eukaryotic genomes give rise to a range of processed and regulated long RNAs that do not appear to code for functional proteins. A subset of these are polyadenylated and typically spliced RNAs transcribed by RNA polymerase II and collectively called long noncoding RNAs (lncRNAs). The recent estimates are that the human genome may have >50,000 distinct lncRNA-producing loci, many of which show tissue-specific activity and dysregulation in human disease, including cancer and neurodegeneration. Given the growing number of lncRNAs implicated in human disease or required for proper development, fundamental questions must be addressed: Which lncRNAs are functional? How is functional information encoded in the lncRNA sequence? Is this information interpreted in the context of the mature or the nascent RNA? What are the specific sequence domains active within lncRNA genes? These are challenging questions, primarily because of the substantial heterogeneity in mechanisms utilized by lncRNAs and the current paucity of lncRNAs with well-understood mechanisms. We are tackling these questions by combination of experimental and computational methods with a focus on lncRNA functions in the brain. I will describe our efforts to decode functional sequence elements in lncRNAs, with a particular focus on the Chaserr/Chd2 and Silc1/Sox11 axes.

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Deciphering gene regulatory elements during inhibitory interneuron differentiation using deep neural

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Yaron Orenstein Department of Computer Science, Bar-Ilan University, Ramat Gan The Mina and Everard Goodman Faculty of Life Sciences, Bar-Ilan University
Ramon Y Birnbaum *Department of Life Sciences, Faculty of Natural Sciences, Ben-Gurion University of the Negev, Beer-Sheva, The Zlotowski Center for Neuroscience, Ben-Gurion University of the Negev, Beer-Sheva.*

During neurogenesis, the differentiation of neuronal progenitors into inhibitory GABAergic interneurons is dependent on the combinatorial activity of transcription factors (TFs) and regulatory elements (REs). However, the roles of TFs and their target REs in inhibitory interneuron progenitors are not fully elucidated. Here, we developed a deep-learning-based framework to identify enriched TF motifs in gene REs (eMotif-RE), such as poised/repressed enhancers and putative silencers. Using epigenetic datasets, we distinguished between active enhancer sequences and non-active enhancer sequences. Using our eMotif-RE framework, we discovered enriched motifs of TFs such as ASCL1, SOX4, and SOX11 in the active enhancer set suggesting a cooperativity function for ASCL1 and SOX4/11 in active neuronal enhancers. We also found enriched ZEB1 and CTCF motifs in the non-active set. Most of the tested putative REs from the non-active enhancer set have no enhancer activity. Two of the eight REs (25%) showed function as poised enhancers in the neuronal system. Moreover, mutated REs for ZEB1 and CTCF motifs increased their activity as enhancers indicating a repressive effect of ZEB1 and CTCF on these REs. Overall, our work integrates a novel framework based on deep learning together with a functional assay that elucidated novel functions of TFs and REs.

Session D6

Chair: Haim Sompolinsky

Israeli German Symposium

Disentangling the Contributions of Vision and Language in Perception and Memory

Galit Yovel, *Tel Aviv University* Adva Shoham, *Tel Aviv University* Idan Grosbard, *Tel Aviv University*

Computational models of face recognition have typically focused on its visual properties. This was the case both for the traditional algorithm that were based on engineered visual features and current deep learning algorithms that are trained on face images. Recent studies have revealed that the representations that are generated by these deep learning algorithms are correlated with human brain and behavioral representation and performance level. However, humans' face recognition goes beyond vision and primarily concerns with the recognition of familiar faces. These faces are represented by both visual and semantic information. In order to model human mental representation of faces we combined visual and semantic (language) deep learning algorithms as well as image-language multi-modal models that generate a visual-semantic representations. We found that all algorithms accounted for human mental representation in perception as well as the representation of the faces in memory. We extended the same findings also to objects. Our findings show that in order to model face and object recognition we should go beyond models that primarily extract visual information. Future computational models that are trained on multi-modal information including dynamic faces and voices are needed to capture additional information that current models overlook.

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Savta's Face: from Visual Perception to Person Knowledge

Winrich Freiwald, *The Rockefeller University*

Jerry Lettvin coined the term Grandmother Neuron in the late 1960s. Lettvin's idea highlights the unique role that faces assume in linking vision to memory: grandmother's face is not simply a specific geometric shape with a particular texture (though it is also that), but a highly important social signal that provides an entry into person knowledge. In the decades ensuing Lettvin's idea, cells with properties akin to and differing from grandmother neurons have been found. Many of these cell's cluster within specialized neural circuits in the primate visual system linking multiple areas with unique functional specializations into a network, to process faces. But these findings left open the question: where and how are familiar faces processed? In my talk I will describe the discovery of a region in primate-specific part of the brain, the temporal pole, that is specialize don the representation of familiar faces. It assumes a position, both computationally and connectomically, in between the generic face-processing network and regions of social cognition. I will present the properties of face representations within the temporal lobe face familiarity area, discuss its role in the overall scheme of face-processing circuitry, and speculate on its role for knowing savta.

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Neuronal mechanisms underlying a single (not just the average) decision

Mathew E. Diamond, *International School for Advanced Studies, Trieste, IT*

Objectives Perceptual knowledge can be quantified by the probability, averaged across many trials, that stimuli will be judged as belonging to their veridical category. Given that real world percepts are unique events, not averages, we seek to dissect individual perceptual judgments.

Methods Experiments involve tactile psychophysics in rats, accompanied by large-scale neural recording/optogenetics. We aim to understand single decisions by identifying three sources of variability and transforming these into controlled experimental variables.

Results We consider: (i) the dynamics of trial history. Single-trial judgment is repulsed by recent stimuli (i.e., more likely to be judged in the opposite category) but attracted by recent choices (more likely to be judged in the same category). These effects are tracked to the frontal cortex. (ii) attention. In a task where rats learn to judge relevant stimuli and ignore irrelevant, the difference in processing of relevant versus irrelevant stimuli also plays out in frontal cortex. (iii) predictions arising from the probabilistic structure of the environment. After imposing non-random reward location sequences, we find that predictions influence perceptual categorization and can be advantageous for ambiguous stimuli.

Conclusions The above results largely generalize to humans. In psychophysics, knowledge about sensory inputs fluctuates, but individual judgments have systematic causes.

Session E2

Chair: Dana Cohen

Rethink about the role of the external globus pallidus in basal ganglia functions

Discharge features of the non-human primate external globus pallidus during sleep

Hagai Bergman, *Hebrew University, Jerusalem*

The external segment of the globus pallidus (GPe) is changing its position as as a mere relay station in the indirect pathway of the basal ganglia (BG) to the central nucleus of the basal ganglia, connecting and effecting both input and output layers of the BG network. Here, I will describe the discharge rate, pattern and synchronization of GPe neurons of non-human primates. GPe neurons can be divided into two distinct populations based on their discharge rate and pattern: low-frequency discharge (LFD-B) and high-frequency discharge with pauses (HFD-P) neurons. I will describe the spontaneous and behaviorally related activity of GPE HFD-P neurons in awake healthy monkeys, during sleep, and following dopamine depletion by the MPTP neurotoxin. Sleep induces significant change in the discharge pattern, however with no significant change of the synchronization of GPe neurons. However, MPTP intoxication, dopamine depletion, and the clinical appearance of Parkinson's symptoms are correlated with massive synchronization of oscillatory activity of GPe neurons.

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Multidimensional encoding in the rodent external globus pallidus

Noam D. Peer, The Gonda Multidisciplinary Brain Research Center, Bar Ilan University
Hagar G. Yamin, The Gonda Multidisciplinary Brain Research Center, Bar Ilan University
Dana Cohen, *The Gonda Multidisciplinary Brain Research Center, Bar Ilan University*

The basal ganglia (BG) play a major role in many daily functions and their malfunction has devastating consequences. To date, the type and the way information is processed and transferred between successive nuclei within the BG remain unclear. The classical view of BG anatomy suggests that information from different cortical areas flows through the BG in segregated circuits along the parallel direct and indirect pathways. We examined how the globus pallidus (GP), a nucleus within the indirect pathway, encodes input from the motor and cognitive domains. We chronically recorded and analyzed neuronal activity in the GP of male rats engaged in a novel environment exposure task. GP neurons displayed multidimensional responses to movement and contextual information. A model predicting single unit activity required many task-related behavioral variables, thus confirming the multidimensionality of GP neurons. In addition, populations of GP neurons, but not single units, reliably encoded the animals' locomotion speed and the environmental novelty. We posit that the GP independently processes information from different domains, effectively compresses it and collectively conveys the stored information to successive nuclei.

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Oscillatory correlations in the globus pallidus explained

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Joshua A. Goldberg, *Department of Medical Neurobiology, the Hebrew University of Jerusalem*

The external globus pallidus (GPe) is a hub in the basal ganglia, whose neurons impose a barrage of inhibitory synaptic currents on neurons of the subthalamic nucleus, substantia nigra, and internal globus pallidus. GPe neurons normally fire independently, but in experimental parkinsonism, they become correlated in the frequency range associated with the pathological rhythms seen in human Parkinson's disease, raising the possibility that they may be generators of the pathological oscillation. We drove individual pallidal neurons with an oscillatory input over a wide range of frequencies. Cross-correlations of these neurons reproduced many of the features seen in parkinsonism, suggesting that their correlated oscillations might derive from a shared input rather than internal interconnections.

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Session E3

Chair: Gadi Gilam, Alexander Binshtok

Modulating pain from the terminal to the brain – Basic and translational insights into mechanisms of pathological pain

THE KINESIN FAMILY MEMBER 2A (KIF2A) GATES NOCICEPTION

Swagata, Dey, Department of Biomolecular Sciences and Department of Molecular Neuroscience, Weizmann Institute of Science Omer Barkai, Department of Medical Neurobiology; Institute for Medical Research Israel-Canada, The Hebrew University-Hadassah School of Medicine, The Edmond and Lily Safra Center for Brain Sciences, The Hebrew University of Jerusalem, F.M. Kirby Neurobiology Center, Boston Children's Hospital and Harvard Medical School, Boston, MA 02115, USA
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Avraham Yaron, *Department of Biomolecular Sciences and Department of Molecular Neuroscience, Weizmann Institute of Science*

Nociceptive axons undergo remodeling as they innervate their targets during development and in response to environmental insults and pathological conditions. How is nociceptive morphogenesis regulated? Here we show that the microtubule destabilizer protein Kif2a is a key regulator of nociceptive terminal structures and pain sensitivity. Ablation of Kif2a in sensory neurons causes hyperinnervation and hypersensitivity to noxious stimuli, whereas touch sensitivity and proprioception

remain unaffected. Computational modeling predicts that structural remodeling is sufficient to explain the observed phenotypes. Furthermore, Kif2a deficiency triggers a transcriptional response comprising a highly specific homeostatic downregulation of specific channels and receptors, thus leading to decrease in hyperexcitability of nociceptive neurons, despite morphological changes. Importantly, this response is correlated with the resolution of pain hypersensitivity. Overall, we reveal a critical control node defining nociceptive terminal structure, which is crucial for regulating nociception.

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Adaptive Changes in the First CNS Nociceptive Neural Network, Leading to Pathological Pain

Ben Title, *Hebrew University of Jerusalem Shaya Lev, Hebrew University of Jerusalem*
Ben Katz, Hebrew University of Jerusalem Shmuel, Hart, Hebrew University of Jerusalem Nurit Engelmayer, Hebrew University of Jerusalem Enrique Velasco Serna, KU Leuven Prudhvi Raj Rayi, Hebrew University of Jerusalem Yosi Yarom, Hebrew University of Jerusalem Alex Binshtok, Hebrew University of Jerusalem

Pathological conditions, such as inflammation or injury, are associated with increased excitability and activity of primary nociceptors. It is unknown how this abnormal input from the periphery affects the output of the first pain-related CNS network, resulting in increased pain perception. To study this, we focused on projection neurons (PNs) of trigeminal nucleus caudalis (TNc) which integrate nociceptive input from trigeminal ganglion nociceptors and local interneurons' activity and transmit an output to higher brain regions. To understand how the output from the TNc is affected by pathological conditions, we characterized PNs intrinsic properties in inflammatory and neuropathic pain models. Surprisingly, during inflammation, PNs displayed reduced excitability (i.e. reduction in input resistance and reduced firing responses), despite increased pain. We suggest that during inflammation, TNc PNs reduce their excitability as an adaptive mechanism to buffer the increased activity from the periphery and transmit a moderate output, and by that minimizing upstream plastic changes, known to occur in chronic pain. Indeed, we show that this adaptive phenomenon does not occur in the chronic neuropathic pain model. In the chronic state, PNs displayed increased firing responses enabling such plastic changes in higher brain centers.

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REINFORCEMENT OF PAIN MODULATION- A MECHANISM BASED TERATEMTN FOR PAIN REFIELF IN CHRONIC PAIN

Irit Weissman-Fogel, *Faculty of Social Welfare and Health Sciences, University of Haifa*

Pain chronification (i.e., the transition from acute to chronic pain) and pain chronicity are accompanied by brain maladaptive plasticity. This causes hypersensitivity of the pain transmitting pathways and reduces the efficiency of the descending pain inhibitory pathways. Non-invasive brain stimulation (NIBS) are neuromodulation techniques that change the activity of the targeted brain areas and inter-connected brain areas, and consequently interfere with neuroplasticity to improve function. In my lecture I will present the current knowledge on how NIBS targeted to the primary motor cortex (M1) modulates the activity of brain areas that are functionally connected with the M1. Specifically, the thalamus and the somatosensory cortex and brain areas that are involved in pain modulation. This results in the suppression of ascending sensory input and improvement of descending pain inhibition. I will also show findings on the modulatory effect of NIBS on the resting-state connectivity of cortico-cortical and cortico-subcortical neural circuits. This is how NIBS-related neuromodulation is linked with improved clinical outcomes in chronic pain patients (e.g., fibromyalgia). Finally, I will present novel findings on the effect of M1 stimulation combined with a behavioral task as a treatment approach for preventing chronic pain.

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The Neural Bases of Emotion Regulation of Pain in Chronic Pain

Gadi Gilam, *Hebrew University of Jerusalem, Israel Jin-Xiao Zhang, Stanford University, United States*
Christine S. Law, Stanford University, United States Kenneth A. Weber II, Stanford University, United States Philippe R. Goldin, University of California Davis, United States Sean C. Mackey, Stanford University, United States James J. Gross, Stanford University, United States

Objectives: Emotion regulation (ER) influences the perception of pain and its chronicity. We aimed to uncover the distinct and shared neural bases of two ER strategies, reappraisal and acceptance, in people with chronic low-back pain (CLBP).

Methods: 188 CLBPs and 38 healthy controls (HC) engaged in reappraisal and acceptance during fMRI and as painful heat was delivered to their lower back. We expected reappraisal and acceptance would engage distinct prefrontal and parietal brain regions, respectively, reduce activiations in similar brain regions associated with pain perception, (e.g., amygdala and insula), and that reappraisal would have stronger effects compared to acceptance.

Results: Reappraisal engaged left-lateralized semantic-prefrontal regions, and reduced pain ratings and activations in the insula and in the nucleus accumbens more than acceptance, that engaged more medial attention-parietal regions. The amygdala did not demonstrate observable effects. No substantial differences emerged between CLBP and HC groups in neuro-behavioral correlates and in ER capabilities. Exploring individual differences in ER success indicated that above and beyond all factors, individuals successful in one strategy were also successful in the other.

Conclusion: Findings confirm distinct and common brain systems engaged in two ER strategies, expanding our understanding of how ER may attenuate pain in chronic pain.

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Session E4

Chair: Ehud Cohen

Cellular proteostasis mechanisms in health and disease

Regulators of α-synuclein secretion and spread in Parkinson's disease

Avraham Ashkenazi, *Tel Aviv University*

There are two main hallmarks of Parkinson's disease (PD) pathology: aggregation and spread of the protein α-synuclein (α-syn) known to form a primary structural component of dense protein-rich and lipid-rich cellular neuronal inclusions called Lewy bodies. Emerging research suggests that lipid membranes have a role in α-syn misfolding and aggregation. Since it may tip the balance between physiological and pathological α-syn, we ask how specific membrane components regulate α-syn aggregation and neuron-to-neuron spread. We established a mouse model to investigate the effect of phospholipids in neuronal membranes on α-syn aggregation and spread and identified novel phospholipid modulators that may be relevant to PD pathology.

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Targeting low levels of MIF expression as a potential therapeutic strategy for ALS

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Mutations in SOD1 cause amyotrophic lateral sclerosis (ALS), a neurodegenerative disease characterized by motor neurons (MNs) loss. We previously discovered that macrophage migration inhibitory factor (MIF), whose levels are extremely low in spinal MNs, inhibits mutant SOD1 misfolding and toxicity. In this study, we show that a single peripheral injection of adeno-associated virus (AAV) delivering MIF into adult SOD1G37R mice significantly improved their motor function, delayed disease progression and extended survival. Moreover, MIF treatment reduced neuroinflammation and misfolded SOD1 accumulation, rescued MNs and corrected dysregulated pathways as observed by proteomics and transcriptomics. Furthermore, we revealed low MIF levels in human induced pluripotent stem cell derived MNs from familial ALS patients with different genetic mutations, as well as in post-mortem tissues of sporadic ALS patients. Our findings indicate that peripheral MIF administration may provide a potential therapeutic mechanism for modulating misfolded SOD1 in vivo and disease outcome in ALS patients.

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A Nucleolar Mechanism Suppresses Proteostasis across the Organism by the Modulation of TGFβ Signaling

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The protein homeostasis (proteostasis) network encompasses a myriad of mechanisms that maintain the integrity of the proteome by controlling various biological functions, including protein folding and degradation. Alas, aging-associated decline in the efficiency of this network enables protein aggregation and consequently the development of late-onset neurodegenerative disorders, such as Alzheimer's disease (AD). Accordingly, the maintenance of proteostasis through late stages of life bears the promise to delay the emergence of these devastating diseases, however, cellular organelles and signaling pathways regulate proteostasis is only partially understood. Here we report that knocking down the activity of the nucleolar FIB-1-NOL-56 complex protects model nematodes from proteotoxicity of the AD-causing Aβ peptide and of abnormally long poly-glutamine stretches. This mechanism promotes proteostasis across tissues by modulating the activity of TGFβ signaling and by enhancing proteasome activity. Our findings highlight the nucleolus as an organismal proteostasis regulator and point at TGFβ as a potential target for the development of new therapies for neurodegenerative maladies.

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Mutation in Protein Kinase A (PRKAR1B) gene drives pathological mechanisms of Neurodegeneration

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Protein Kinase A (PKA) neuronal function is controlled by the interaction of a regulatory (R) subunit dimer to two catalytic (C) subunits. Recently, the L50R variant in the gene encoding to the RIβ subunit was identified in individuals with a novel neurodegenerative disease. However, the mechanisms driving the disease phenotype remained unknown. We reveal that RIβ is an aggregation-prone protein that progressively accumulates in wildtype and Alzheimer's mouse models with age, while aggregation is accelerated in the RIβ-L50R mouse model. We define RIβ-L50R as a causal mutation driving an age-dependent behavioral and disease phenotype in human and mouse models. Mechanistically, this mutation disrupts RIβ dimerization, leading to aggregation of its monomers. Intriguingly, interaction with the C-subunit protects the RIβ-L50R from self-aggregating, in a dose-dependent manner. Furthermore, cAMP signaling induces RIβ-L50R aggregation. This study sheds light on a remarkably under-appreciated common mechanism across neurodegenerative diseases driven by mutations at dimer interface.

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UFMylation regulates proteostasis in C. elegans

Reut Bruck-Haimson and Prof. Ehud Cohen

Hebrew University

The maintenance of protein homeostasis (proteostasis), by supervising the integrity of protein synthesis, folding, and the direction of misfolded polypeptide for degradation, is vital for cellular and organismal health. Malfunction of the proteostasis network (PN) leads to the accumulation of toxic protein aggregates which are tightly associated with the development of various late-onset neurodegenerative disorders. These include Alzheimer's disease (AD) and the group of polyglutamine (polyQ) expansion disorders such as Huntington's disease (HD). Post-translational modifications (PTMs) play key roles in proteostasis maintenance, and UFMylation, a ubiquitin-like PTM, is emerging as a significant modulator of these processes. Using the nematode Caenorhabditis elegans as a model organism, we discovered that UFMylation changes with age and is influenced by the insulin/insulin-like growth factor signaling (IIS) pathway, a key regulator of aging. Knocking down components of the UFMylation pathway, such as ufm-1 and uba-5, protected worms from the toxicity of Aβ3-42 and polyQ35-YFP, and slightly extended their lifespans. Interestingly, UFMylation knockdown reduced the levels of Aβ3-42 aggregates as well as of SDS-resistant polyQ35-YFP aggregates. Immuno-precipitation followed by proteomic analysis indicated that UFMylation is enriched in ribosomal, chromatin-remodeling, and cytoskeletal proteins, as well as in phagosome-related proteins which are involved in protein transport and clearance. An RNAi-based screen for some of the identified proteins revealed that the protective effects of UFMylation knockdown were closely tied to chaperones (HSP-1, HSP-90, SIP-1), the motor protein kinesin-19, and CAR-1, suggesting these proteins are necessary for UFMylation's role in stress mitigation. To

test how the reduction of UFMylation affects the transcriptomic landscape of worms that are challenged by Aβ3-42 proteotoxicity we performed an RNA sequencing experiment and found that UFMylation knockdown is associated with upregulation of genes that their products mediate immune defense and suppression of genes that are involved in reproduction, particularly in germline cells. Many of these transcriptional changes were linked to DAF-16 and HSF-1, both are well-established aging and stress responses controlling transcription factors, which are needed for the protective effect of UFMylation knockdown. These findings highlight UFMylation as a pivotal regulator of aging and proteostasis, involving chaperones, motor proteins, and transcriptional networks, and suggest its potential as a therapeutic target for neurodegenerative and age-related diseases.

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Session E5

Chair: Oren Shriki

Artificial neural networks as models of biological sensory processing

SENSORY RECURRENT NETWORKS: OPTIMAL INFORMATION REPRESENTATION, HALLUCINATIONS, AND SYNAESTHESIA

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

The specific role of recurrent connections in cortical sensory processing remains largely undefined. This presentation will introduce a neural network model wherein the recurrent connections evolve based on specified learning rules, with the aim of optimizing the network's information representation. These networks are designed to adapt to varying input statistics, and under numerous conditions, they trend towards a near-critical state, specifically operating on the precipice of hallucinations. Moreover, under certain scenarios, such as a decrease in external inputs or an increase in neural plasticity, the network may transition into a hallucinatory state. The theory will be illustrated through applications to models of a visual hypercolumn, tinnitus, and synaesthesia. References: Shriki O. and Yellin D., Optimal Information Representation and Criticality in an Adaptive Sensory Recurrent Neural Network. PLoS Computational Biology 12(2): e1004698, 2016 Shriki O., Sadeh Y. and Ward J., The Emergence of Synaesthesia in a Neuronal Network Model via Changes in Perceptual Sensitivity and Plasticity. PLoS Computational Biology 12(7): e1004959, 2016 Dotan, A., & Shriki, O., Tinnitus-like “hallucinations” elicited by sensory deprivation in an entropy maximization recurrent neural network. PLoS Computational Biology, 17(12), e1008664, 2021.

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DISENTANGLING REPRESENTATIONAL GEOMETRIES IN NEURAL NETWORK MODELS OF HUMAN PERCEPTION

Tal Golan, *Department of Cognitive and Brain Sciences, Ben-Gurion University of the Negev; Zuckerman Institute, Columbia University*
Wenxuan Guo, Department of Psychology, Columbia University Heiko, Schütt, University of Luxembourg; Zuckerman Institute, Columbia University
Nikolaus Kriegeskorte, Departments of Psychology, Neuroscience, and Electrical Engineering, Zuckerman Institute, Columbia University

Neural or behavioral responses to a stimulus set can be characterized by their pairwise representational distances (i.e., dissimilarities). This level of description, representational geometry, provides an important bridge between human perceptual representations and neural network models. By comparing dissimilarities estimated from human behavior or neuroimaging to those estimated from artificial neural networks, we can assess computational hypotheses about perceptual representation. However, as modeling advances, a new challenge emerges multiple models often predict the human representational geometries equally well. Fortunately, the image-computable nature of these models presents a solution: the synthesis of stimulus sets designed to effectively distinguish between alternative representational models. We elucidate the methodological challenge and our proposed solution using human-face representation as a case study. We demonstrate that randomly sampled face stimuli fail to elicit distinct representational geometries in neural networks trained on different computational tasks, thereby impeding model discrimination in behavioral and fMRI experiments. By morphing faces to yield distinct similarity relations in different models, we generated stimulus sets designed for efficient model discrimination. Upon applying these stimulus sets empirically; we uncovered evidence for a computational mechanism involving a generative model of human faces underlying both behavioral similarity judgments and right fusiform face area hemodynamic activation patterns.

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Aligned and oblique dynamics in recurrent neural networks

Omri Barak, *Technion*

The relation between neural activity and behaviorally relevant variables is at the heart of neuroscience research. When strong, this relation is termed a neural representation. There is increasing evidence, however, for partial dissociations between activity in an area and relevant external variables. While many explanations have been proposed, a theoretical framework for the relationship between external and internal variables is lacking. Here, we utilize recurrent neural networks (RNNs) to explore the question of when and how neural dynamics and the network's output are related from a geometrical point of view. We find that RNNs can operate in two regimes: dynamics can either be aligned with the directions that generate output variables, or oblique to them. We show that the magnitude of the readout weights can serve as a control knob between the regimes. Importantly, these regimes are functionally distinct. Oblique networks are more heterogeneous and suppress noise in their output directions. They are furthermore more robust to perturbations along the output directions. Finally, we show that the two regimes can be dissociated in neural recordings. Altogether, our results open a new perspective for interpreting neural activity by relating network dynamics and their output.

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Rethinking backpropagation: training large neural networks with low-dimensional error signals

Jonathan Kadmon, *Hebrew University, Jerusalem*

Traditional deep network training relies on high-dimensional error signals that backpropagate through the network, a computationally intensive and biologically implausible process. However, given that most tasks are inherently low dimensional, the original error signal should reflect this simplicity. In this talk, I will present an alternative approach that leverages low-dimensional error signals for training large neural networks, challenging prevailing assumptions about the complexity needed for effective learning. I will introduce a novel learning rule based on Feedback Alignment, which allows us to control error signal dimensionality by decoupling feedback from the forward pass. Our findings show that even minimal error dimensionality—comparable to task dimensionality—can efficiently train networks. Understanding low-dimensional error feedback is crucial for modeling perceptual pathways in the brain, where error signals are often restricted and arrive through indirect pathways. For instance, in a simple model of the ventral visual pathway, training with low-dimensional error signals produces center-surround receptive fields, mirroring those found in the retina. This approach suggests that incorporating low-dimensional error signals could lead to more computationally efficient and biologically realistic models of sensory processing, offering new insights into brain function.

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Session E6

chair: Dori Derdikman, Yaniv Ziv

Learning and Memory: From mice to humans

In Search of Engrams: Single neuron recordings and deep brain stimulation in the human temporal lobe

Itzhak Fried, MD, PhD

Neurosurgical opportunities to record and stimulate single-neuron activity in people who can declare their thoughts, offer a unique window into the biology of learning and memory. I will present neuronal codes for space, time and objects in the human temporal lobe expressed by single neuron and population activity in the hippocampal-entorhinal circuitry and discuss recent data on modulation of this system during wake-sleep cycles to enhance encoding and consolidation of memory. The prospects of editing human memories by enhancement, inception or deletion of specific content raise therapeutic possibilities and ethical concerns.

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Short term memory in freely moving mice

Eran Stark, *Sagol Department of Neurobiology, Haifa University, Haifa*

Short term memory (STM) can be explicit (working memory) or implicit (priming). Primate studies suggest that explicit sensory STM involves neocortical networks, and rodent work indicates that explicit spatial STM involves the hippocampus. However, whether sensory STM involves the hippocampus is unknown, and there is no rodent model for priming. To study explicit STM, we developed a delayed whisking-based discrimination task for freely moving mice. After mice learned the task, we used closed loop optogenetic control to transiently silence the bilateral dorsal CA1 during memory maintenance. Compared to interleaved control blocks, success rate degraded during silencing blocks. To study implicit STM, we trained other freely moving mice to discriminate between low and high pure long tones and to ignore short pure tones. Presenting short and long tones in succession, we found that success rate was lower when tone pairs were congruent, both being high or both low, compared with incongruent tone pairs. Thus, the hippocampus appears to be necessary for explicit sensory STM, and mice enjoy the same benefit as humans from prior exposure to associated stimuli.
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Active experience, not time, determines within day representational drift in dorsal CA1

Dori Derdikman, *Technion*

hippocampal representations of space are continuously updated, inducing drift. This drift is related to the subject's active experience within a context rather than the passage of time. This suggests that the hippocampus is engaged in the continuous reconsolidation of active memories.

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The Naming of Nonhuman Primates, Hints about the Evolution of Human Langua

David Omer, *The Hebrew University of Jerusalem*

The ability to vocally label conspecifics is a hallmark of advanced cognitive function, previously thought to be unique to humans and dolphins. However, the evolutionary origins of this ability in primates remain poorly understood. Addressing this gap, we investigated whether non-human primates can exhibit vocal labeling of conspecifics. Using machine learning analyses of naturally occurring phee call dialogues in marmoset monkeys, combined with real-time playback experiments, we demonstrate for the first time that marmosets use phee calls to vocally label conspecifics. Our findings reveal that marmosets not only perceive and correctly respond to calls directed at them, but also that family members share similar calls to label conspecifics. Moreover, vocal learning plays a crucial role, as marmosets acquire these vocal labels from their family group. These results provide novel insights into vocal communication in nonhuman primates and its possible relevant evolutionary trajectory to human language .

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Causal role of insular cortex neuronal activity manifolds in appetitive and aversive learning

Ayal Lavi, Dept. of Brain Sciences, *Weizmann Institute of Science*
Yoav Livneh, Dept. of Brain Sciences, Weizmann Institute of Science

Learning and storage of associations between external and internal sensory information have long been known to require the insular cortex (InsCtx). Indeed, these associations are thought to underline InsCtx's involvement in diverse behaviors, from feeding and drinking that shape nutritional preferences, to anxiety and addiction that regulate adaptive behaviors. We recently revealed stereotyped InsCtx neuronal population activity patterns (i.e., neuronal manifolds) that are associated with specific physiological needs (e.g., thirst) and predict need-fulfillment. However, the differential involvement of InsCtx activity patterns in appetitive and aversive learning, and their causal role in mediating related behaviors, remain unclear. How do InsCtx neuronal manifolds evolve during learning and what is their causal role in behavioral choice? We address these questions with an all-optical approach using longitudinal two-photon imaging and holography. We tracked the same InsCtx ensembles across learning and assessed the stability of different representations. Our findings demonstrate that learning alters the structure of the InsCtx neuronal manifold in a state-dependent manner. Moreover, we observed unique manifold patterns that vary based on the sensory modality of appetitive and aversive stimuli. To elucidate the causal relationship between InsCtx activity and behavior, we employed targeted holographic optogenetic stimulation of need- and stimulus-specific neuronal ensembles. Holographic recreation of naturally-occurring activity patterns ("on-manifold" stimulation) uncovers their causal role in network dynamics and related behaviors. In contrast, artificially generated holographic patterns ("off-manifold" stimulation) induce long-term plasticity and modifies network dynamics. Furthermore, the effects of "on-manifold" stimulation are highly dependent on the animal's physiological state. Based on these observations, we are currently investigating both the causal role of specific InsCtx activity patterns, as well as the effects of artificially induced network plasticity. Our findings contribute to our evolving understanding of how the brain integrates sensory information with internal states to guide adaptive behaviors, with potential implications for disorders involving maladaptive learning and nutritional decision-making processes.

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The Movie After-Effect: Widespread Activity-Dependent Renormalization Revealed during Ecological Stimuli in the Human Cortex

Niv Yahav - Faculty of Electrical Engineering, Holon Institute of Technology, Holon
Rafael Malach* - Department of Brain Sciences, Weizmann Institute of Science
Erez Simony* - *Faculty of Electrical Engineering, Holon Institute of Technology, Holon, Israel Department of Brain Sciences, Weizmann Institute of Science, Rehovot*
* Equal Contribution

How does the human brain maintain a stable range of neural responses during dynamic naturalistic experiences? Here, we report on a widespread renormalization process revealed across 300 cortical regions, as the brain transitions from movie viewing to post-movie rest. Our study was based on 7T-fMRI data from the Human Connectome Project, where 170 subjects watched 14 movie clips with 20-second resting intervals in between clips. Specifically, we found that most of the voxels that were highly activated at the end of movie clips, displayed a pronounced inactivation that persisted throughout the 20-sec rest period following those movies. By contrast, voxels that were suppressed by the movie showed a rebound activation above the resting state baseline. Interestingly, classification of the resting-state intervals across subjects, at a long latency (20 seconds) following the termination of the movie, successfully identified the movie clips that preceded the rest interval, revealing that the renormalization during rest was informative about the prior activation pattern. In conclusion, our study reveals a widespread, cortical "movie-after effect" (MvAE), suggesting a ubiquitous adaptive recalibration mechanism following dynamic ecological stimuli. The persistence of information about a response during rest may further serve an important role in short-term memory.

Session F1

Chair: Gadi Blumrosen

Monitoring and Diagnostics of neurological disease and disorders at home environment settings

Research and Development of digital parameters for functional and cognitive assessment

Hadas Lewy Head of Digital Health Vventures, *Holon Institute of Technology Holon*

As demographics changes and the population age, medicine is moving towards the P4 medicine: Predictive, Preventive Proactive and Personalized. This approach will provide a personalized care with proactive preventive care, early detection, timely intervention and disease management that will improve care and QoL. Cognitive and functional assessment and early intervention can prevent deterioration and enable the patient to live independently at home. For healthcare system, alerts and AI based Decision Support Systems (DSS) are important tools for management of large ageing population in providing personalized proactive treatment. Digital Biomarkers and AI-based tools for cognitive and functional assessment are being developed with the aim to transfer the commonly used cognitive tests into objective, digital tests that can be used in different settings and will provide better understanding on the disease progression. Multidisciplinary team using research protocols in a unique infrastructure of four research labs at HIT. We use agile research approach and clinical trials for collection of Patient Generated Data (PGD), from unobtrusive sensors for identification of patients at risk, prediction of patients' deterioration and alert for early intervention. Our research, using different approaches for cognitive and functional assessment can be used to replace some of the healthcare professional's' work and provide them with powerful tools for assessment, follow-up and timely intervention. These tools can be used at different settings for better screening and treatment of the older population. The presentation will discuss the research approach and possible impact on the ageing populations as well as on future care models.

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Evaluating changes in dexterity in people with Parkinson's disease at home using an electric piano

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Hila Tamir-Ostrover, *Department of Physical Therapy, Faculty of Medical & Health Sciences, School of Health Professions, Tel Aviv University, Tel Aviv*
Sharon Hassin-Baer, *Movement Disorders Institute and Department of Neurology, Chaim Sheba Medical Center, Tel Hashomer, Ramat-Gan & Faculty of Medical & Health Sciences, Tel Aviv University, Tel Aviv*
Tsvia Fay-Karmon, *Movement Disorders Institute and Department of Neurology, Chaim Sheba Medical Center, Tel Hashomer, Ramat-Gan & Faculty of Medical & Health Sciences, Tel Aviv University, Tel Aviv*

One of the symptoms of Parkinson's disease is a reduction in dexterity, which can lead to difficulties in performing actions of daily living. There is some preliminary evidence that learning to play the piano can help people with Parkinson's disease improve in their dexterity. As bringing people to the clinic or lab for training is often a significant barrier, in this pilot study we had participants perform most of the piano practice at home using a provided digital piano, with exercises and compliance facilitated using video chat. Several dexterity tests were performed before and after the six-week training program to test dexterity changes, and some dexterity improvements were observed in the pilot participants. We will describe the setup used including novel recording devices, and present the dexterity tests used and their interpretation.

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Home-based assessment of Parkinson's disease severity with facial video recording using AI and clinical knowledge

Harel Rom, *Tel Aviv Sourasky Medical Center and Tel Aviv University*
Ori Peleg, *Tel Aviv Sourasky Medical Center and Tel Aviv University*
Anat Mirelman, *Tel Aviv Sourasky Medical Center and Tel Aviv University*
Gaddi Blumrosen, *Holon Institute of Technology (HIT)*
Inbal Maidan, *Tel Aviv Sourasky Medical Center and Tel Aviv University*

Background: Early diagnosis of Parkinson's disease (PD) can assist in designing efficient treatments. Reduced facial expressions are considered a hallmark of PD, and therefore, advanced Artificial Intelligence (AI) image processing can be a non-invasive tool for PD detection.
Objective: To determine the sensitivity of image-to-text AI, which matches facial frames recorded in home settings with descriptions of PD facial expressions, in identifying disease.
Methods: Facial image of 67 PD patients and 52 healthy-controls (HCs) were collected via standard video recording. Using clinical knowledge, we compiled descriptive sentences detailing facial characteristics associated with PD. The facial images were analyzed with OpenAI's CLIP model to generate probability scores, indicating the likelihood of each image matching the PD-related descriptions. Results: The image-to-text AI showed the best results in identifying PD patients based on the facial expression item (AUC=0.78±0.05), especially at the 'mild' stage (AUC=0.87±0.04). The motor MDS-UPDRS score followed (AUC=0.69±0.05), while the total MDS-UPDRS score showed the lowest performance (AUC=0.59±0.05). Regression analysis of PD severity scores revealed correlations with MDS-UPDRS components ($r>0.23$, $p<0.0001$).
Conclusions: Our results highlight the feasibility of advanced AI in clinical diagnosis, suggesting a novel approach for home-based screening to identify PD patients. This method represents a significant innovation, transforming clinical knowledge into practical algorithms that can serve as effective screening tools.

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Behavioral Based Neurological condition assessment: roadmap, and feasibility with ADHD diagnosis from real-life video

Gaddi Blumrosen, *School of Computer science, Faculty of Exact Science, Faculty of Digital Medical Technologies, Faculty of Data Sciences, Holon Institute of Technology, Holon, Israel*

Continuous assessment of medical condition at home environment plays an important role in fields of neurological diseases and disorders diagnostics. Traditionally the assessment is limited to the clinic environment, exploit medical care resources, require subject travel time, suffers from clinician bias, and do not reflect all patient condition at natural environment. In this work, we suggest exploiting existing daily life accessories to extract behavioral patterns that can be used to derive neurological biomarkers to different diseases and disorders. We review existing sensing and processing methods, define criterion for sufficient, efficient and reliable sensing, analyze the computational resources in relation to user comfort, continuity in time and space, and the level of activity context awareness. We further show feasibility of the approach with estimation of ADHD severity from real-life video clip. A pre-trained deep learning framework was used to extract upper body skeleton joints coordinates over time, and then dynamic spatial- temporal features. We then used different prediction models for ADHD recognition and scoring. The results of this work can be used for continuous assessment of neurological condition ADHD severity at real-life home settings, can assist as an additional evaluation tool for clinician and assist the clinician in treatment planning and in optimizing medication type and dose in ADHD and other neurological diseases.

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Leveraging Artificial Intelligence to Enhance Alexithymia Assessment: Exploring the Potential of Large Language Models

Hila Gvirts, *Psychology department, Ariel University, Israel*
Gaddi Blumrosen, *Computer and data science department, Holon institute of Technology, Israel*
Olivier Luminet, *Research Institute for Psychological Sciences, UC Louvain, Louvain-la-Neuve, Belgium*

Objectives Alexithymia is a personality trait characterized by difficulties in identifying emotions, recognizing the connection between emotions and bodily sensations, effectively communicating feelings to others, and an externally-oriented way of thinking. Typically, the TAS-20 self-report questionnaire is used to assess alexithymia. However, evaluating this trait can be difficult because individuals with alexithymia often lack self-awareness of their own emotions. Therefore, using information obtained from daily life communication through advanced AI models can provide a continuous assessment of alexithymia in individuals' natural environments.

Methods We conducted video interviews with 20 participants (10 males, 10 females). The interviewer audio was extracted from the recordings and transcribed to text using audio-to-text software. Using a well-trained Large Language Model (LLM), we employed an AI-based approach to evaluate participants' levels of alexithymia. We compared the results obtained from the LLM assessment to participants' self-reported scores on the 20-item Toronto Alexithymia Scale (TAS-20), including subscale scores and thel total score. mportantly, we assessed the LLM's performance in two scenarios: one where the model based its predictions solely on the TAS-20 responses, and another where the model utilized its vast knowledge of human psychology and behavior to make its assessments.

Results The results show that the LLM model's predictions based on its own knowledge were significantly more accurate and consistent than its

predictions based solely on the TAS-20 responses. This suggests that the LLM was able to leverage its comprehensive understanding of human emotions and behavior to better assess alexithymia than the standard self-report measure.

Conclusions This research demonstrates the feasibility of using AI LLM models for accurate and consistent evaluation of alexithymia. Further studies are needed with a larger population and longer time intervals to validate these findings. The technology offers continuous assessment of alexithymia, saving time and resources, and reducing bias compared to the traditional assessment. Importantly, the superior performance of the LLM when using its own knowledge highlights the potential of AI-based approaches to provide more objective and accurate evaluations of complex personality traits like alexithymia compared to traditional questionnaire-based methods. Finally, this work has the potential to develop clinical decision support tools for objective evaluation.

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Sleep physiological biomarkers derived from continuous seamless monitoring sleep stages abnormalities at home

Joachim Behar, *Technion-IIT Faculty of Biomedical Engineering*

Background: Sleep staging is a fundamental component in the diagnosis of sleep disorders and the management of sleep health. Traditionally, this analysis is conducted in clinical settings and involves a time-consuming scoring procedure. Recent data-driven algorithms for sleep staging, using the photoplethysmogram (PPG) time series, have shown high performance on local test sets but lower performance on external datasets due to data drift. Methods: This study aimed to develop a generalizable deep learning model for the task of four class (wake, light, deep, and rapid eye movement (REM)) sleep staging from raw PPG physiological time-series. In order to create a more generalizable representation, we developed and evaluated a deep learning model called SleepPPG-Net2, which employs a multi-source domain training approach. SleepPPG-Net2 was benchmarked against two state-of-the-art models. Results: SleepPPG-Net2 showed consistently higher performance over benchmark approaches, with generalization performance (Cohen's kappa) improving by up to 21%. Performance disparities were observed in relation to age, sex, and sleep apnea severity. Conclusion: SleepPPG-Net2 sets a new standard for staging sleep from raw PPG time-series.

Session F2

Chair: Lior Mayo

Here and Back Again, A Neuroimmunology's Tale

Mapping the immune response in the aging gut at the setting of stroke

Eran Blacher, *Hebrew University*

Age-associated changes in gut permeability are likely to regulate immune response in the elderly, particularly in the setting of stroke. While most of the data on experimental stroke comes from young mice, We study the contribution of the intestinal immune system to post-stroke inflammation in aged mice. In aged mice, stroke causes a prolonged and sustained gut barrier breach that provokes intestinal immune response, leads to translocation of microbial components across the epithelial barrier and results in exacerbated neurological damage. In aging, maladaptive intestinal immune response aggravates gut permeability, leading to exacerbated systemic inflammation and a severer brain damage. We determined that impaired metabolism in a specific subtype of intestinal macrophages may delay intestinal permeability resolution in aging. In these intestinal macrophages, the lipid messenger PGE2 is a major modulator of immune responses. Its binding to EP2 receptor suppresses metabolism and consequent beneficial myeloid functions. Myeloid-specific deficiency of the EP2 receptor reduced post-stroke gut barrier breach and systemic inflammation by blocking monocytes recruitment form blood to the post-stroke intestinal lamina propria. These results highlight that myeloid cell reprogramming from EP2 inhibition can ameliorate immune cell responses in the aged gut, leading to a better neurological recovery after stroke.

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A neuro-endocrine-immune perspective to age-related neurodegenerative disorders

Alon Monsonego, *Ben-Gurion University*

Aging is generally characterized as a gradual increase in tissue damage, associated with cell senescence, low-grade systemic inflammation and increased incidence of age-related diseases. The extent to which tissue damage originates from a gradual decline in immune regulation, which consequently compromises the body capacity to repair damages, has not been fully explored. In this lecture, I will describe the lifespan accumulation of specific dysregulated immune cell subsets in both human and mouse models of aging and disease, their functional properties and their coevolution with systemic inflammation in the process of declined immunity and tissue repair capacity with age. These will be discussed in the context of pubertal-induced thymus involution, dysregulation of hormonal systems such as the hypothalamus-pituitary-adrenal (HPA) and the hypothalamus-pituitary-gonadal (HPG) axes, as processes that culminate at driving age-related neurodegenerative diseases. Early biomarkers and therapeutic strategies will be discussed.

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Herpes Simplex Virus-1 Proteins Drive Alzheimer's disease Pathologies in Humans

Vanesa R. Hyde 1, Chaoming Zhou 1, Krishnashis Chatterjee 1, Juan Fernandez 1, Pururav Ramakrishna 1, Amanda Lin 1, Gregory Fisher 1, Orhan Tunç Çeliker 1, Jill Caldwell 2, Omer Bender 3, Paul R. Kinchington 4 Daniel Z. Bar 3, Leonardo D'Aiuto 2 and Or A. Shemesh 1

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DNA and RNA of Herpes Simplex Virus 1 (HSV-1) were found in the brains of Alzheimer's disease (AD) patients. The molecular presence of HSV-1 in AD is intriguing as HSV-1 virions are rarely detected in AD brains. To follow the link between HSV-1 and AD, we imaged viral proteins in postmortem human AD brains using expansion microscopy, a method that physically expands tissues by a factor of 4.5x, allowing a 40 nm imaging resolution, and immunolabeled herpetic proteins, AD pathologies and cell markers. We found an abundance of herpetic proteins across large brain areas. Importantly, we found that HSV-1 proteins strongly co-localized with AD pathologies. Consequently, we hypothesized that expression of HSV-1 proteins may lead to AD pathology. As a complementary system to the fixed human brain slices, we introduced HSV-1 in human derived brain organoids and imaged the relationships between viral proteins and the formation of AD pathologies via expansion microscopy. We found that HSV-1 infection triggered these pathologies, pointing out that viruses may be triggers of immune responses driving AD. This study sheds light on one common pathogen, HSV-1, while serving as a framework to unveiling molecular causation between infectious agents and AD hallmarks.

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Dissecting the effects of distinct VTA projections on peripheral immunity

Itay Zalayat, Hilla Azulay-Debby, Megan Sammons, Shir Barak, Margarita Sirotkin, Zeinab Zbeidat, Dorit Farfara, Nadia Boshnak, Eden Avishai, Asya Rolls,

Technion

The Ventral Tegmental Area (VTA) is a crucial part of the brain's reward system and regulates motivated behavior. Studies have shown that activation of VTA dopaminergic (DA) neurons can stimulate anti-bacterial and anti-tumor immunity, linking mental states to immune responses. However, the specific mechanisms behind these effects are unclear. Given that VTA-DA neurons project to multiple brain regions, each promoting different behaviors, we considered that the immune effects of each projection might also be distinct. In this study, we used retro-DREADD manipulations to investigate the contributions of VTA projections to the Nucleus Accumbens (NAc), medial prefrontal cortex (mPFC), and basolateral amygdala (BLA) in immune regulation. Our results show that each projection affects the peripheral immune response to infection differently. Notably, VTA-mPFC projections have an opposing effect on the anti-bacterial immune response compared to VTA-BLA projections. Surprisingly, VTA projections to the NAc had limited impact on the peripheral immune response. We also examined the downstream anatomical connections of each projection using anterograde viral tracing, which shed light on the mechanisms behind the immune effects. These findings help understand the role of VTA pathways in immune regulation and may aid in developing diagnostic and therapeutic strategies for immune pathologies.

Session F3

Chair: Gilad Silberberg, Ilan Lampl

Structure and function of interhemispheric communication

Behavioral states control binocular vision through input-specific mechanisms

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Ivo Spiegel, Department of Brain Sciences and department of molecular neuroscience Weizmann Institute of Science, Rehovot, Israel

Binocular vision is essential for depth perception and goal-directed behaviours such as navigation and prey hunting - however, under certain behavioural conditions, reduced binocular and enhanced monocular (i.e. peripheral) vision might serve an animal's behavioural demands better. Whether binocular vision undergoes behavioural state-dependent changes is not known, yet classic studies indicate that binocularity in the adult visual cortex is fixed. By combining multi-modal behavioural tracking and calcium imaging in excitatory neurons in the binocular zone of the primary visual cortex of adult mice, we find that (1) the binocularity of single neurons and binocular vision are not fixed but rather change rapidly according to an animal's arousal state, and (2) these state-dependent changes are driven by input-specific enhancements of sensory responses rather than by state-dependent changes in eye position or pupil dilation. Thus, since inputs to neurons in the visual cortex monocular zone are strengthened at high arousal, these findings indicate that the relative impact of binocular vision from the centre of the animal's visual field decreases at high arousal while the impact of peripheral monocular vision increases which, in turn, adapts an animal's visual perception to its behavioural demands e.g. to better perceive an approaching danger.

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Projections from the claustrum to the frontal cortex modulate performance and cortical representation of an attention demanding task

Peretz-Rivlin N., Fatal Y., Levin S., Yvgi I. & Citri A.

Hebrew University

The vast reciprocal connectivity of the claustrum with most of the brain, and specifically with the frontal cortex, is one of its major properties; proposing it as a leading candidate in modulating global cortical changes. Interested in the claustrum's role in cognitive processes, we have previously demonstrated that the activity of ACC projecting claustral neurons is associated with engagement i.e. the degree to which sensory percepts trigger actions.

In this work I aimed to understand the mechanism behind the seen effects, specifically focus on the action of ACCp claustral neurons on the cortex. To this end I recorded extracellular neural activity from the frontal cortex, using Neuropixels probes, in mice performing a delayed cue-go task with an auditory distractor, while ACCp claustral neurons were optogentically activated during task and at rest.

Analysis of the collected dataset reveals robust and significant responses of the majority of recorded cortical neurons to claustrum optogenetic activation. In addition, claustrum activation seems to have a prolonged effect where control mice's behavioral responses tend to improve and become more selective over repeated experimental session, while experiment mice don't show that trend. Moreover, cortical representation of the task parameters both is single units and LFP activity matches individual mice performance in the task, and support the hypothesis that claustrum manipulation disrupts adaptive representation.

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Reduction of corpus callosum activity during whisking leads to interhemispheric decorrelation

Yael Oran, Department *of Neurobiology, Weizmann Institute of Science*
Yonatan ,Katz Michael, Sokoletsky Katayun ,Cohen-Kashi Malina1 & Ilan, Lampl

Interhemispheric correlation between homotopic areas is a major hallmark of cortical physiology and is believed to emerge through the corpus callosum. However, how interhemispheric correlations and corpus callosum activity are affected by behavioral states remains unknown. We performed laminar extracellular and intracellular recordings simultaneously from both barrel cortices in awake mice. We find robust interhemispheric correlations of both
spiking and synaptic activities that are reduced during whisking compared to quiet wakefulness.
Accordingly, optogenetic inactivation of one hemisphere reveals that interhemispheric coupling occurs only during quiet wakefulness, and chemogenetic inactivation of callosal terminals reduce interhemispheric correlation, especially during quiet wakefulness.
Finally, using two-photon calcium imaging, we demonstrate that spontaneous callosal activity is lower during whisking in an opposite manner to the local population. Our results provide important insight into the causal role of the corpus callosum in mediating interhemispheric communication, as well as its dependence on the behavioral state

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Branch-specific spike failures at distal axons in mouse cortex in vivo

Netanel Ofer, Victor-Hugo Cornejo, Rafael Yuste, *Columbia University*

The propagation of action potentials along axons is traditionally considered to be reliable. However, there is debate, based on experimental or simulation-based studies, on whether some spikes fail to invade all axonal branches. Given the complex morphologies of axonal trees, characterized by extensive branching and long-distance projections, spike failures could be functionally important. To address this, we used axon-GCaMP6s to record action potential at axonal branching points in mouse cortical pyramidal neurons in vivo. We activated axons using an extracellular electrode in the mouse somatosensory cortex, varying stimulation frequencies. Our observation revealed spike failures in a subset of branches, as a function of spike frequency. These findings suggest that axonal morphologies contribute to signal processing in the cortex.

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Strategies for transferring higher order information across hemispheres

Elad Avidan, Shlomo David Sherer, Shaked Yadlin, Rotem Goldschmidt, Ariel Gilad,
PI, *Medical neurobiology and faculty of medicine, Hebrew University*

Interhemispheric information transfer is vital for our perception of the world. While sensory information and working memory (WM) process in one hemisphere have been extensively studied, the transfer of sensory information between hemispheres remains poorly understood. We trained mice to distinguish between two types of textures on both sides of their whiskers in a go/no-go task. Once the mice reached expert level, we introduced a delay period between texture presentations, requiring them to retain and transfer WM of the first stimulus to the other hemisphere. Using dual-hemisphere wide-field calcium imaging, we analyzed the dynamics of interhemispheric transfer.

We found the involvement of the Barrel cortex (BC) in processing choice-information rather than type-information and sequential activity across hemispheres in posterior areas during the early delay period where left posterior area (P) initially held the sensory and type-information and subsequently transferred it to the homotopic P area. Moreover, we found additional posterior areas such as the posterior-medial (VISpm) and the retrosplenial-dorsal (RD) involved in the transfer of WM. Finally, using support vector machine (SVM) and optogenetics we outline the sequence contributes to the decision based on the sensory input, and we suggest a model for interhemispheric transfer.

Session F4

Chair: Michal Rivlin

Coding principles in sensory and motor systems: breaking the rules

Battle of the memories – how the brain prevents the co-formation of conflicting memories.

Julia E. Manoim*, Tel Aviv University Tal Camchy, Tel Aviv University Hadas Lerner, Tel Aviv University* Ran Darshan, *Tel Aviv University* Moshe Parnas*, Tel Aviv University*

How information is integrated across different forms of learning is crucial to understand higher cognitive functions. Animals form classic or operant associations between cues and their outcomes. It is believed that a prerequisite for operant conditioning is the formation of a classical association. Thus, both memories coexist and are additive. However, the two memories can result in opposing behavioral responses, which can be disadvantageous. We show that Drosophila classical and operant olfactory conditioning rely on distinct neuronal pathways leading to different behavioral responses. Plasticity in both pathways cannot be formed simultaneously. If plasticity occurs at both pathways, an interference between them occurs and learning is disrupted. Importantly, activity of the navigation center is required to prevent plasticity in the classical pathway and enable it in the operant pathway. These findings fundamentally challenge hierarchical views of operant and classical learning and show that active processes prevent coexistence of the two memories.

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Reliability and Stability of Tactile Perception in Rodents

Rony Azouz, *Ben Gurion University*

Rodents rely on their whiskers as vital sensory tools for tactile perception, enabling them to distinguish textures and shapes. Ensuring the reliability and constancy of tactile perception under varying stimulus conditions remains a fascinating and fundamental inquiry. This study explores the impact of stimulus configurations, including whisker movement velocity and object spatial proximity, on texture discrimination and stability in rats. Through a textures' discrimination task, rats of both sexes exhibited consistent discrimination performance irrespective of changes in stimulus configuration. However, alterations in stimulus configuration significantly affected the rats' ability to maintain stability in texture perception. Additionally, we investigated the influence of stimulus configurations on cortical neuronal responses by manipulating them experimentally. Notably, cortical neurons demonstrated substantial and intricate changes in firing rates without compromising the ability to discriminate between textures. Nevertheless, these changes resulted in a reduction in texture stability. These findings emphasize the importance of considering multiple factors and their interactions when studying the impact of stimulus configuration on neuronal responses and behavior. Understanding the complex relationships in tactile perception enhances our knowledge of sensory processing. It sheds light on how animals maintain reliable perception amidst variable stimulus conditions.

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High-Dimensional Encoding of Movement by Single Neurons in Basal Ganglia Output

Mati Joshua, *Hebrew University*

The Substantia Nigra pars reticulata (SNpr), an output structure of the basal ganglia, has been hypothesized to gate the execution of movements. Previous studies focusing mostly on saccadic eye movements have reported that SNpr neurons are tonically active and either pause or increase their firing during movements, consistent with the gating role. We recorded activity in the SNpr of two monkeys during smooth pursuit and saccadic eye movements. SNpr neurons exhibited highly diverse reaction patterns during pursuit, including frequent increases and decreases in firing rate, uncorrelated responses in different movement directions and in reward conditions resulting in the high dimensional activity of single neurons. These diverse temporal patterns surpassed those in other oculomotor areas in the frontal cortex, basal ganglia, and cerebellum. These results suggest that temporal properties of the responses enrich the coding capacity of the basal ganglia output beyond gating or permitting movement.

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Home-based assessment of Parkinson's disease severity with facial video recording using AI and clinical knowledge

Harel Rom, *Tel Aviv Sourasky Medical Center and Tel Aviv University* Ori Peleg, *Tel Aviv Sourasky Medical Center and Tel Aviv University* Anat Mirelman, *Tel Aviv Sourasky Medical Center and Tel Aviv University* Gaddi Blumrosen, *Holon Institute of Technology (HIT)* Inbal Maidan, *Tel Aviv Sourasky Medical Center and Tel Aviv University*

Background: Early diagnosis of Parkinson's disease (PD) can assist in designing efficient treatments. Reduced facial expressions are considered a hallmark of PD, and therefore, advanced Artificial Intelligence (AI) image processing can be a non-invasive tool for PD detection. Objective: To determine the sensitivity of image-to-text AI, which matches facial frames recorded in home settings with descriptions of PD facial expressions, in identifying disease. Methods: Facial image of 67 PD patients and 52 healthy-controls (HCs) were collected via standard video recording. Using clinical knowledge, we compiled descriptive sentences detailing facial characteristics associated with PD. The facial images were analyzed with OpenAI's CLIP model to generate probability scores, indicating the likelihood of each image matching the PD-related descriptions. Results: The image-to-text AI showed the best results in identifying PD patients based on the facial expression item (AUC=0.78±0.05), especially at the 'mild' stage (AUC=0.87±0.04). The motor MDS-UPDRS score followed (AUC=0.69±0.05), while the total MDS-UPDRS score showed the lowest performance (AUC=0.59±0.05). Regression analysis of PD severity scores revealed correlations with MDS-UPDRS components ($r>0.23$, $p<0.0001$). Conclusions: Our results highlight the feasibility of advanced AI in clinical diagnosis, suggesting a novel approach for home-based screening to identify PD patients. This method represents a significant innovation, transforming clinical knowledge into practical algorithms that can serve as effective screening tools.

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Light-Responsive Neurons in the Medial Prefrontal Cortex Encode Light Intensity

Elyashiv Zangen, Shira Hadar, Christopher Lawrence, Mustafa Obeid, Hala Rasras, Ella Hanzin, Ori Aslan, Eyal Zur, Nadav Schulcz, Daniel Cohen-Hatab, Yona Samama, Sarah Nir, Yi Li, Irina Dobrotvorskia & Shai Sabbah

Objectives: The medial prefrontal cortex (mPFC) regulates emotional and cognitive processes, and has been linked to psychiatric and addiction disorders. Effects of light on several such mPFCdependent processes suggest that mPFC networks may possess light sensitivity. However, no light-intensity encoding was hitherto revealed in the mPFC. Methods: By combining mapped extracellular recordings from the mPFC of awake mice with chemogenetic manipulations, we traced a pathway driving mPFC neuronal light-evoked responses. Results: Over half of captured mPFC neurons responded to light, and in 15%, steady-state firing rate changed monotonically along light-intensity steps and gradients. Intensity-encoding neurons were divisible into four types, two enhancing and two suppressing their firing rate with increased light intensity. Intensity encoding depended predominantly on intrinsically photosensitive retinal ganglion cells (ipRGCs) signalling, transmitted through the thalamic perihabenular nucleus (PHb). The four types were also found in the PHb, where they exhibited shorter latency and increased sensitivity compared to their mPFC counterparts. Finally, within the mPFC, light exposure suppressed prelimbic activity but enhanced infralimbic activity, mirroring similar opposition in these subregions' roles in fear conditioning, drug-seeking, and anxiety. Conclusions: The displayed prefrontal light-intensity processing is postulated to represent a substrate of light-susceptibility of mPFC-mediated functions.

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Mixed connectivity and local computations across a whole adult Drosophila brain

Amit Gross and David Deutsch, *department of neurobiology, University of Haifa*

Mapping connections between neurons can be achieved by analyzing electron microscopic images of the brain. Recently, a comprehensive neuronal wiring diagram of an entire adult female Drosophila melanogaster brain was published, detailing 139,255 neurons and approximately 50 million chemical synapses. While the brain can be represented as a network of nodes (neurons) connected by edges (synapses), neurons themselves possess complex morphologies, and these morphological details influence network computations. In this study, we examined the distribution of presynaptic and postsynaptic terminals within individual cells across the connectome and discovered that many Drosophila neurons exhibit mixed connectivity. This means they contain presynaptic terminals within dendrites and postsynaptic terminals within axons. Although axo-dendritic synapses—presynaptic axons connecting to postsynaptic dendrites—are predominant, other types, such as axo-axonic and dendro-dendritic synapses, are also prevalent. We identified that approximately 10% of neuron-neuron connections are axo-axonic and 3% are dendro-dendritic. These non-canonical connections vary depending on brain region, cell type, neurotransmitter, and the morphology of pre- and postsynaptic partners. Our detailed analysis suggests that non-canonical connections frequently participate in local recurrent circuits and that localized segregation of pre- and postsynaptic terminals occurs within dendritic and axonal trees. Together, our whole-brain connectome analysis highlights the complexity of neural connectivity, indicating that non-canonical connections are widespread and may play a key role in local computations.

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Session F5

Chair: Abed Mansour , Zeev Melamed

Stem-cells based technologies to study brain disorders

Seeking Convergence and Divergence between Autism and Schizophrenia using genomic tools and iPSC patient derived neurons

Eva Romanovsky. *Sagol department of neurology, University of Haifa*
Ashwani Choudhary, *department of neurology, University of Haifa*
Ahmad Abu Akel, *School of Psychological Sciences, University of Haifa*
Shani Stern, *Sagol department of neurology, University of Haifa*

Autism spectrum disorders (ASDs) are a highly heritable and complex group of psychiatric conditions that occur during early childhood. The patients exhibit abnormal repetitive behaviors and impairment in communication and cognitive skills. Recent efforts have led to unmasking some of the genetic and environmental risk factors that contribute to the manifestation of ASD. Previous studies have focused on the genetic correlations between ASDs and other neuropsychiatric disorders but an in-depth understanding of the common variants is required. In this study, we have conducted an extensive analysis of the common variants identified in ASDs by Genome-wide association studies (GWAS) and compared it to the consensus genes and single nucleotide polymorphisms (SNPs) of Schizophrenia (SCZ) to determine the shared genetic associations of these disorders. Furthermore, using a meta-analytical approach we have also probed the cellular phenotypes observed in ASD and compared it to the phenotypes observed in SCZ using induced pluripotent stem cell (iPSC) models. Our collective analysis of the deficits in ASD in comparison to SCZ iPSC-derived neurons indicates the presence of developmental divergent trajectories of neuronal pathophysiology that converge to similar phenotypes after the neuronal cells have matured, even though the disorders share a high percentage of genetic mutations.

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Rescue of impaired axonal regeneration in iPSC-derived motor neurons with TDP-43 pathology

Zevik Melamed, *Department of Medical Neurobiology, Faculty of Medicine at the Hebrew University*

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disorder characterized by loss of upper and lower motor neurons, leading to progressive, fatal paralysis and respiratory failure. ALS is associated with cytoplasmic aggregation and nuclear clearance of the RNA-binding protein TDP-43 in affected neurons. We recently identified a new critical role for TDP-43 in regulating stathmin-2 (STMN2), a neuronal microtubule-associated protein essential for axon growth and regeneration. Reduction of TDP-43 suppresses stathmin-2 levels by uncovering a premature polyadenylation and cryptic splice-site in stathmin-2 pre-mRNA, producing a truncated non-functional RNA.

Here, we identified the mechanisms through which TDP-43 sustains normal stathmin-2 pre-mRNA processing and used those insights to develop methods to restore stathmin-2 synthesis. In iPSC-derived motor neurons affected by TDP-43 dysfunction, utilizing antisense oligonucleotides (ASOs) that block cryptic splicing, restored stathmin-2 level and rescued impaired axonal regeneration capacity after injury. Notably, loss of stathmin-2 in adult mice was sufficient to drive axonal collapse, muscle denervation and a corresponding collection of motor phenotypes. Finally, using mice gene-edited to contain the human stathmin-2 cryptic exon, we establish that ASO-injection into cerebral spinal fluid is a viable approach to rescue stathmin-2 levels in neurodegenerative diseases - especially ALS and FTD - affected by TDP-43 pathology.

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Modeling Neurological Disorders at the Blood Brain barrier (BBB)

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The blood brain barrier (BBB) is a multicellular neurovascular unit where central nervous system (CNS) cells interact with brain microvascular endothelial cells (BMECs). BMECs form a specialized transporter barrier, permitting passage of essential molecules to the CNS while blocking harmful factors and most drugs. BBB dysfunction is linked to neurological disorders, highlighting the need to understand its physiology in health and disease. However, animal models' limited relevance due to species-specific differences in BBB properties necessitates a human-relevant BBB model.

We combined induced pluripotent stem cells (iPSC) and Organ-on-Chip technologies, developing a platform with isogenic iPSC-derived BMECs (iBMECs), astrocytes, and neurons that mimic human BBB functionalityat the organ-level. The BBB-on-Chip exhibits physiological barrier functions and faithfully predict CNS penetrability.

Using this model, we studied the rare psychomotor disability MCT8-deficiency. Impaired thyroid hormone (TH) transport across the BBB was identified as an underlying cause. Thus, MCT8 re-expression at the BBB is a potential translational approach. Pre-clinical testing of BBB-targeted gene therapy by intravenous delivery of AAV9-MCT8 in a mouse model of MCT8-deficiency resulted in a nearly complete rescue of TH brain content, gene expression, and long-term psychomotor and cognitive improvements. These studies pave the way for a future clinical trial.

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Organellomics: AI-driven deep organellar phenotyping reveals novel ALS mechanisms in human neurons

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Systematic assessment of organelle architectures, termed the organellome, offers valuable insights into cellular states and pathomechanisms, but remains largely uncharted. Here, we present a pipeline for deep phenotypic learning using vision transformers, resulting in the Neuronal Organellomics Vision Atlas (NOVA) model that studies 3 million confocal images of 25 distinct membrane-bound and membraneless organelles in human neurons. Our organellomics approach evaluates cellular phenotypes by quantifying changes in the localization and morphology of multiple organelles, and by consolidating information across organelles it yields an integrated depiction of cellular state. We reveal significant interactions between cytoplasmic mislocalized TDP-43 — a hallmark of ALS — and processing bodies (P-bodies), membraneless organelles that regulate mRNA stability, which is confirmed through patient-derived neurons and human neuropathology. Furthermore, organellomics delineates phenotypic changes in neurons carrying ALS-associated mutations and demonstrates diagnostic potential for patient-derived neurons. Together, organellomics offer a novel approach to studying the neuro-cellular biology of diseases.

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HIKESHI-related Hypo-myelinating Leukodystrophy: a Brain-On-Chip model for pre-clinical testing of gene therapy

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HIKESHI Hypomyelinating Leukodystrophy (HHL) is an ultra-rare devastating and life-threatening neurodegenerative disease. HHL patients suffer from severe psychomotor disability and microcephaly. Disturbingly, HHL patients have severe reactions to febrile illness, leading to symptomatic worsening and even death. HIKESHI is known to be involved in nuclear shuttling of Heat Shock Protein 70 (HSP70) to protect cells against heat-stress (HS) induced damage. Thus, impairments in this function may potentially explain degeneration and death following febrile illnesses in patients.
Most HHL patients are Ashkenazi Jewish (AJ) descendants with a homozygous p. V54L missense mutation in the HIKESHI gene. While heterozygous mutations have a prevalence of 1:200 in the AJ population, only a handful of HHL patients were identified to date. A Hikeshi knockout model was reported as neonatally lethal. Thus, there is an unmet need for the development of robust disease-relevant models that would allow studying underlying mechanisms and test potential therapeutic approaches.
We have identified a novel p.P78S pathogenic variant in a Palestinian Christian Arab (PCA) family. We have generated induce pluripotent stem cells (iPSCs) from the PCA patients, from two AJ patients, and from their sex-matched family relatives. We exposed undifferentiated iPSCs to HS and found that HHL patients have significantly reduced HIKESHI protein levels following HS. This was accompanied by impaired translocation of HSP70 to the nuclei. In order to test this effect in disease-relevant cells, we have differentiated our comprehensive set of HHL-iPSCs to NESTIN-positive motor neuron precursor cells, which also exhibited a similar impairment in the ability of HSP70 to translocate to the nucleus. Using this basis we intend to develop a Brain-on-Chip platform to test whether a gene therapy approach can reverse this phenotype.

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Immunocompetent Human Midbrain Organoids to Study Neuroinflammation in Parkinson's Disease

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Parkinson's Disease (PD) is a severe neurodegenerative disorder which is characterized by significant loss of dopaminergic neurons in the midbrain. Neuroinflammation is recognized as a major pathological feature underlying neurodegeneration in PD, highlighting possible disease mechanisms associated with microglial dysfunction. However, neuroinflammatory mechanisms involved in PD pathogenesis are not fully understood. There is a pressing need for a human-specific model system that contains both neural and immune components to investigate microglia-mediated neuroinflammation in PD. Human midbrain organoids (hMBO) are a pluripotent stem cell (PSC)-derived 3D cultures that largely mimics the midbrain in terms of cellular composition, organization, and function. Yet, current organoid systems lack immune cells, limiting their application to study neuroinflammation in neurodegenerative diseases. To address this challenge, we developed immunocompetent hMBOs by co-culturing PSC-derived microglia with hMBO under defined conditions. Our results reveal that microglia can efficiently incorporate into hMBOs, be maintained for extended period, and express microglia-specific markers. In summary, we report a novel approach for the generation of microglia-containing midbrain organoids that can be used as a platform for basic and translational research applications.

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Session F6

Chair: Yoav Livneh

Brain-body interactions in the insular cortex

Insular cortex circuits mediating flexible feeding behaviors

Maria Olvera Caltzontzin, Sebastien Bullich,
Darielle Lewis-Sanders, Sarah Stern,
MPFI

Feeding is a complex motivated behavior, which is regulated by the body's energy demands, but also be external factors such as emotion, palatability, and cognition. However, the mechanisms by which this regulation of feeding occurs is not well understood. We recently found a population of neurons in the insular cortex marked by Nitric Oxide Synthase-1 (Nos1), which are required for a form of non-homeostatic feeding, which is potentiated by food-associated cues in the environment. These neurons project to the central amygdala, and are active during food consumption bouts. Nevertheless, the mechanisms by which Nos1 regulates feeding is not well understood. Here, using a combination of chemogenetics and in vivo calcium imaging, we tested the role of Nos1 neurons in a variety of other food-related, learning, and anxiety tasks. We find that Nos1 neurons specifically regulated learned-feeding behaviors, likely by signaling the homeostatic relevance of food in the environment. Furthermore, using monosynaptic rabies tracing and tissue clearing, we find that Nos1 neurons receive inputs from a number of areas, including sensory and motor cortices, basolateral amygdala and areas of the brainstem. Future studies will investigate the role of these projections in regulating flexible feeding behaviors.

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Interoceptive predictions during hunger and thirst in the insular cortex

Yael Prilutski, Dr. Yoav Livneh, *Weizmann Institute of Science*

The Insular cortex (InsCtx) encompasses within it the primary interoceptive cortex, receiving visceral signals of the internal body state. The neural mechanisms underlying the representation of distinct physiological needs and the role of the InsCtx in creating interoceptive predictions remain unclear. Here, we established a novel behavioral system combined with InsCtx two-photon imaging to explore how InsCtx represents caloric and fluid deficiencies (hunger and thirst) and need-relevant food and water rewards.

We examined the activity of large populations of InsCtx neurons across multiple days and need states. Our results demonstrate that ongoing InsCtx activity represents the current physiological state, with a stable, distinct representation of hunger and thirst. InsCtx population responses to food/water rewards reflected predictions of future anticipated satiety. InsCtx predictions were rigid, with responses to reward omissions closely resembling actual reward consumption..

To identify the inputs that contribute to InsCtx representation of current and future need states, we optogenetically inhibited axons from visceral thalamus (VPM/VPLpc) in InsCtx while imaging InsCtx activity during water/food consumption. Our preliminary data suggest that VPM/VPLpc information is essential for creating interoceptive predictions of future satiety.

Our results provide insights into InsCtx's role in processing physiological needs and related interoceptive predictions.

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Brain-body interactions: Sensations and predictions in the insular cortex

Yoav Livneh, *Weizmann Institute of Science*

The brain and body are in a continuous dialog that is essential for our physical and mental health. Little is known about how this dialog is achieved at the neurobiological level. A large corpus of work implicates the insular cortex as a central node for bi-directional brain-body communication. However, direct evidence for its functional role is scarce. We developed a microprism-based cellular imaging approach to monitor insular cortex activity in behaving mice across different physiological need states. We combine this imaging approach with manipulations of peripheral physiology and related brainstem and hypothalamic circuits to investigate the underlying mechanisms. I will first present our recent data suggesting that insular cortex population activity represents both current bodily states, as well as future predicted ones. These predictions of future states are rigid as they are not easily updated by incoming sensory inputs. I will then focus on our current efforts to understand these predictions under conditions of conflicting physiological needs, and the potential role of these predictions in regulating bodily physiology.

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CORTICAL INTEROCEPTIVE PREDICTIONS FOR NEURAL CONTROL OF NUTRITIONAL CHOICE

Stav Shtiglitz, Dr. Yoav Livneh, *Weizmann institute of science*

Homeostasis and health require continuous bidirectional brain-body communication, which relies on interoception, the perception of internal bodily signals.

The brain uses past and present interoceptive information to anticipate future changes and guide behavior. Several studies point to the insular cortex (InsCtx) as a key player in these processes.

Here, we investigated InsCtx's role in guiding nutrient intake, focusing on consumption of sugar, an essential energy source.

We established an operant task in which mice use olfactory cues to guide consumption of naturally or artificially sweetened solutions. Initially, mice exhibited equal preference, yet within a few days, they identified and preferred sugar. This preference persisted even after switching cue-outcome associations or reducing palatability with a bitter tastant. Hence, this preference is likely due to the association with positive post-ingestive signals.

We used longitudinal two-photon imaging to track the same InsCtx populations at various stages of learning and re-learning. We examined InsCtx's representations of taste, post-ingestive nutrients, and interoceptive predictions. Our preliminary analyses suggest a robust representation of sugar consumption that emerges after learning, independent of taste, potentially reflecting an interoceptive prediction of post-ingestive sugar absorption. Understanding InsCtx activity patterns could shed light on its role in vital brain-body interactions.

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Intra-insula Circuit Mediates the Association between External and Internal Sensory Information

Kobi Rosenblum, *Sagol Department of Neuroscience, Center for Gene Manipulation in the Brain, University of Haifa*

Conditioned taste aversion, a pavlovian conditioning procedure, can be acquired using different tastes as conditioned stimulus and different sick inducing agents as unconditioned stimulus. The insular cortex, a brain region that integrates internal and external information, is necessary for conditioned taste aversion. However, underlying cellular mechanisms within the insula enabling the formation and retrieval of the association are not known.

Taking together the fact that taste and its valence are encoded in the anterior insular cortex, and that aversive related information are represented in the posterior insula, we demonstrated that a bi-directional circuit connecting the anterior and posterior insula mediates different facets of the conditioned taste aversion. Our study demonstrate that this newly described intra-insular circuit specifically modulates the interaction between bodily state and taste information.

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Immunoception: immune representation in the brain

Asya Rolls, *Technion IIT, Technion Institute of R&D*

Increasing evidence indicates that the brain regulates peripheral immunity, yet whether and how the brain represents the state of the immune system remains unclear. We found that the brain's insular cortex stores immune-related information. In this talk I will discuss how the representation formed in the insular cortex interacts with other brain areas and examine what potential information can be stored uniquely in the insular cortex

Session F6

Chair: Yoav Livneh

Conding principles in sensory and motor system: breaking the rules

Battle of the memories – how the brain prevents the co-formation of conflicting memories.

Julia E. Manoim, Tal Camchy, Hadas Lerner, Ran Darshan, Moshe Parnas,
Tel Aviv University

How information is integrated across different forms of learning is crucial to understand higher cognitive functions. Animals form classic or operant associations between cues and their outcomes. It is believed that a prerequisite for operant conditioning is the formation of a classical association. Thus, both memories coexist and are additive. However, the two memories can result in opposing behavioral responses, which can be disadvantageous. We show that Drosophila classical and operant olfactory conditioning rely on distinct neuronal pathways leading to different behavioral responses. Plasticity in both pathways cannot be formed simultaneously. If plasticity occurs at both pathways, an interference between them occurs and learning is disrupted. Importantly, activity of the navigation center is required to prevent plasticity in the classical pathway and enable it in the operant pathway. These findings fundamentally challenge hierarchical views of operant and classical learning and show that active processes prevent coexistence of the two memories.

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Reliability and Stability of Tactile Perception in Rodents

Rony Azouz, *Ben Gurion University*

Rodents rely on their whiskers as vital sensory tools for tactile perception, enabling them to distinguish textures and shapes. Ensuring the reliability and constancy of tactile perception under varying stimulus conditions remains a fascinating and fundamental inquiry. This study explores the impact of stimulus configurations, including whisker movement velocity and object spatial proximity, on texture discrimination and stability in rats. Through a textures' discrimination task, rats of both sexes exhibited consistent discrimination performance irrespective of changes in stimulus configuration. However, alterations in stimulus configuration significantly affected the rats' ability to maintain stability in texture perception. Additionally, we investigated the influence of stimulus configurations on cortical neuronal responses by manipulating them experimentally. Notably, cortical neurons demonstrated substantial and intricate changes in firing rates without compromising the ability to discriminate between textures. Nevertheless, these changes resulted in a reduction in texture stability. These findings emphasize the importance of considering multiple factors and their interactions when studying the impact of stimulus configuration on neuronal responses and behavior. Understanding the complex relationships in tactile perception enhances our knowledge of sensory processing. It sheds light on how animals maintain reliable perception amidst variable stimulus conditions.

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High-Dimensional Encoding of Movement by Single Neurons in Basal Ganglia Output

Mati Joshua, *Hebrew University*

The Substantia Nigra pars reticulata (SNpr), an output structure of the basal ganglia, has been hypothesized to gate the execution of movements. Previous studies focusing mostly on saccadic eye movements have reported that SNpr neurons are tonically active and either pause or increase their firing during movements, consistent with the gating role. We recorded activity in the SNpr of two monkeys during smooth pursuit and saccadic eye movements. SNpr neurons exhibited highly diverse reaction patterns during pursuit, including frequent increases and decreases in firing rate, uncorrelated responses in different movement directions and in reward conditions resulting in the high dimensional activity of single neurons. These diverse temporal patterns surpassed those in other oculomotor areas in the frontal cortex, basal ganglia, and cerebellum. These results suggest that temporal properties of the responses enrich the coding capacity of the basal ganglia output beyond gating or permitting movement.

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Positional information drives distinct traits in transcriptomically identified neuronal types

Inbal Shainer, *Johannes M. Kappel, Eva Laurell, Joseph C. Donovan, Martin Schneider,* Enrico Kuehn*, Irene Arnold-Ammer, Manuel Stemmer, Johannes Larsch, Herwig Baier*

Neuronal phenotypic traits such as morphology, connectivity, and function are dictated, to a large extent, by a specific combination of differentially expressed genes. Clusters of neurons in transcriptomic space correspond to distinct cell types and in some cases (e.g., C. elegans neurons and retinal ganglion cells) have been shown to share morphology and function. The vertebrate optic tectum is composed of a spatial array of neurons that transform visual inputs into motor outputs. While the visuotopic map is continuous, subregions of the tectum are functionally specialized. To uncover the cell-type architecture of the tectum, we transcriptionally profiled its neurons, revealing approximately 60 cell types that are organized in distinct anatomical layers. We then measured the functional tuning of thousands of neurons to a battery of ethologically relevant visual stimuli by two-photon calcium imaging and matched them to their cell-type identities. Surprisingly, we found that neurons that are transcriptionally similar can diverge functionally and morphologically. Incorporating the spatial coordinates of neurons within the tectal volume as a classifier revealed functionally defined subclusters within individual transcriptomic clusters. Our findings suggest that extrinsic, position-dependent factors expand the phenotypic repertoire of genetically similar neurons.

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Light-Responsive Neurons in the Medial Prefrontal Cortex Encode Light Intensity

Elyashiv Zangen, Shira Hadar, Christopher Lawrence, Mustafa Obeid, Hala Rasras, Ella Hanzin, Ori Aslan, Eyal Zur, Nadav Schulcz, Daniel Cohen-Hatab, Yona Samama, Sarah Nir, Yi Li, Irina Dobrotvorskia & Shai Sabbah , *Hebrew University*

Objectives: The medial prefrontal cortex (mPFC) regulates emotional and cognitive processes, and has been linked to psychiatric and addiction disorders. Effects of light on several such mPFCdependent processes suggest that mPFC networks may possess light sensitivity. However, no
light-intensity encoding was hitherto revealed in the mPFC.
Methods: By combining mapped extracellular recordings from the mPFC of awake mice with chemogenetic manipulations, we traced a pathway driving mPFC neuronal light-evoked responses.
Results: Over half of captured mPFC neurons responded to light, and in 15%, steady-state firing rate
changed monotonically along light-intensity steps and gradients. Intensity-encoding neurons
were divisible into four types, two enhancing and two suppressing their firing rate with increased light intensity. Intensity encoding depended predominantly on intrinsically photosensitive retinal ganglion cells (ipRGCs) signalling, transmitted through the thalamic
perihabenular nucleus (PHb). The four types were also found in the PHb, where they exhibited shorter latency and increased sensitivity compared to their mPFC counterparts.
Finally, within the mPFC, light exposure suppressed prelimbic activity but enhanced infralimbic activity, mirroring similar opposition in these subregions' roles in fear conditioning, drug-seeking, and anxiety.
Conclusions: The displayed prefrontal light-intensity processing is postulated to represent a substrate of
light-susceptibility of mPFC-mediated functions.

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Mixed connectivity and local computations across a whole adult Drosophila brain

Amit Gross and David Deutsch, *department of neurobiology, University of Haifa*

Mapping connections between neurons can be achieved by analyzing electron microscopic images of the brain. Recently, a comprehensive neuronal wiring diagram of an entire adult female Drosophila melanogaster brain was published, detailing 139,255 neurons and approximately 50 million chemical synapses.
While the brain can be represented as a network of nodes (neurons) connected by edges (synapses), neurons themselves possess complex morphologies, and these morphological details influence network computations.

In this study, we examined the distribution of presynaptic and postsynaptic terminals within individual cells across the connectome and discovered that many Drosophila neurons exhibit mixed connectivity. This means they contain presynaptic terminals within dendrites and postsynaptic terminals within axons. Although axo-dendritic synapses—presynaptic axons connecting to postsynaptic dendrites—are predominant, other types, such as axo-axonic and dendro-dendritic synapses, are also prevalent. We identified that approximately 10% of neuron-neuron connections are axo-axonic and 3% are dendro-dendritic. These non-canonical connections vary depending on brain region, cell type, neurotransmitter, and the morphology of pre- and postsynaptic partners.
Our detailed analysis suggests that non-canonical connections frequently participate in local recurrent circuits and that localized segregation of pre- and postsynaptic terminals occurs within dendritic and axonal trees.

Together, our whole-brain connectome analysis highlights the complexity of neural connectivity, indicating that non-canonical connections are widespread and may play a key role in local computations.

POSTERS

Topic 1

Coding and decision making : Motor planning

Relating Dynamics of Hidden Neural States in Canary HVC to Changes in Their Song Syntax

Keinan Poradosu, *Weizmann Institute of Science*
Dr. Yarden Cohen, Weizmann Institute of Science

Canary song is a flexible sequential behavior composed of trilled repetitions of syllables called phrases. These phrases are flexibly ordered following long-range syntax rules that generate a huge repertoire of songs. Projection neurons (PNs) in the canary premotor nucleus HVC were shown to reflect hidden states; activity that is time-locked to specific phrase types and modulated by past song contexts. This encoding of song history was shown to preferentially occur in transitions that follow long-range syntax rules, which we term complex transitions. Our current working model is that HVC retains information about past song history that is readily available to enact history dependent phrase transitions. However, the dynamics of this neural encoding across days, and its correlation with changes in behavior remain unknown. Here, by tracking the same HVC PNs across months using calcium imaging with miniaturized head-mounted microscopes, we begin to elucidate the relationship between dynamics of hidden neural states and canaries' changing syntax rules. We show initial observations that information about song history in HVC PNs prior complex transitions correlates to the syntactic dependence of the transition across days.

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Investigation of pathway downstream of striatum reveals potential non-canonical role of SNr in behavioral initiation

Mohammad Tamimi, *Hebrew University*
David Lipton, Itay Shalom, Tomer Sheinfeld, Ben Gonzales, and Ami Citri

The substantia nigra pars reticulata (SNr) (along with the globus pallidus externus (GPe)) is central to the basal ganglia's role in motor behavior modulation, processing complex neural inputs to orchestrate motor control. In the traditional basal ganglia model the direct pathway inhibits the SNr to facilitate action selection. Recent findings challenge this straightforward dichotomy, suggesting more nuanced interactions within these pathways. Utilizing optogenetics and fiber photometry, our study traces calcium activity in SNr neurons receiving inputs from either the orofacial-associated ventrolateral-striatum (VLS) or the lower-limb-associated dorsolateral-striatum (DLS) as freely-moving mice perform orofacial behaviors. Surprisingly, we observed a significant increase in activity in VLS-associated SNr neurons that predominantly correlates with the initiation of orofacial behaviors. This result was surprising given the well-documented activity of canonically SNr-suppressing, direct pathway striatal-neurons coincident with behavior initiation. There was also an increase in activity in DLS-associated neurons, though slightly less pronounced and temporally aligned with the full-body component of orofacial behaviors, such as pre-lick posture-adjustment and body-turning before body licking. These results indicate that the SNr may require robust activity to selectively inhibit directly competing behaviors, rather than uniformly suppressing unrelated actions. We are now turning our attention to GPe neurons downstream VLS and DLS.

Topic 2

Cognition: Decision Making

Winner-take-all fails to account for pop-out accuracy

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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 research suggests that winner-take-all mechanisms have limited ability to gather information even from large populations, thus its role in pop-out visual search is non-trivial. To address this topic, we studied the winner-take-all from the perspective of a readout mechanism and investigated the accuracy in which it can detect the deviant stimulus. We found that the performance of the winner-take-all cannot account for the high accuracy found in behavioral experiments. On the one hand, the inherent neuronal heterogeneity prevents the winner-take-all to accumulate information from large populations. On the other hand, the accuracy of a generalized population-based winner-take-all algorithm is limited by the widely reported noise-correlations. Our result raises the question of whether our fundamental understanding of the underlying mechanism of pop-out visual search can account for the observed behavior.

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Continuous decision making in a closed-loop auditory navigation task

Shai Yellinek, *ELSC HUJI*

Itai Wasserman, ELSC HUJI, Robert Reiner, ELSC HUJI Eran Lottem, ELSC HUJI

A central goal in neuroscience is to understand the neural basis of perceptual decision-making behavior. Traditionally, this is studied through paradigms that focus on discrete behavioral events, like pressing a lever or licking a water spout, in response to isolated stimuli. In these paradigms, both stimuli and actions are sparse, with information flowing in one direction - from stimulus to action - without feedback from actions influencing subsequent stimuli. In contrast, natural behavior is inherently different; it is continuous and involves an ongoing cycle of perception-action loops, where animals not only respond to stimuli but also actively influence them in the process. In this work, we present a novel task that engages mice in a continuous sensory-control task, allowing us to investigate the neural mechanisms behind naturalistic decision-making. Our closed-loop auditory-navigation task requires mice to search for a random target location in an open arena to receive water rewards. They rely on an auditory stimulus - a pure tone whose frequency continuously changes depending on the mouse's orientation relative to the target. Consequently, the stimuli that guide behavior are also continuously changed by it. We begin by showing that mice learn to perform this challenging task by using sound cues to guide their movements and locate targets efficiently. We then introduce a series of manipulations to the stimulus structure within the environment, demonstrating that mice are capable of adaptive responding to a continuously changing input stream within dynamic closed-loop settings. To investigate the role of cortical processing in this behavior, we pharmacologically inhibited the auditory cortex using focal application of the GABA-A receptor agonist muscimol. This inhibition produced a contralateral bias in sound sensitivity with minimal impact on overall locomotion. Based on these findings, we propose a computational framework involving cortico-striatal circuits to support continuous, sensory-driven control of locomotion.

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INHIBITION MEDIATES THE ROLE OF THE dACC DURING GAIN AND LOSS MOTIVATED LEARNING

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Reinforcement Learning (RL) is a fundamental learning process that involves updating one's beliefs about the environment. It was hypothesized that different brain mechanisms execute reward and punishment RL, yet the nature of the punishment RL is not clear(Lake et al. 2019). MRS enables the non-invasive measurements of glutamate (Glu) and g-aminobutyric-acid (GABA), which modulate a wide range of cognitive and behavioral processes, including RL(Bezalel, Paz, and Tal 2019). We examine the dynamics of both GABA and Glu in the dACC, which is engaged in RL, while performing an RL task during appetitive and aversive conditions. 111 healthy volunteers were scanned on a 7T scanner while performing RL tasks under negative and positive motivation. Both MRS and BOLD fMRI data were acquired. We find that during the positive RL, GABA is negatively correlated with learning scores and the BOLD from the dACC and the putamen. However, under the negative RL, GABA significantly increases and no longer correlates with BOLD or behavior, yet shows an inverse correlation with the dACC-putamen connectivity. We suggest that inhibition mediates the role of the dACC during gain- and loss-motivated learning. This work emphasizes the contribution of spectroscopic data to our understanding of neuronal mechanisms underlining decision-making.

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THE EFFECT OF COMMERCIALS ON THE NEURAL SIGNAL OF VALUE

Inbal Gur-Arie, *School of Psychological Sciences Adam Hakim, Sagol School of Neuroscience, Tel Aviv University*

Dino Levy, Sagol School of Neuroscience, Tel Aviv University and Coller School of Management, Tel Aviv University

Objectives: A basic aim of marketing research is to predict consumers' preferences and the success of marketing campaigns. Previously, we developed a deep learning model to predict subject's preferences for pictures of products based on their EEG data. Here, we extend this method to video commercials.

Methods: First, subjects viewed products and indicated their willingness to pay (WTP) for each product. Afterward, subjects viewed commercials for these same products, indicated their WTP for each product, and ranked how much they liked the commercial. We recorded subjects' brain activity using EEG during these first two parts. A week later, subjects again indicated their WTP for the products, without EEG recordings.

Results: We found that watching commercials increased subjects' WTP. Commercials' liking and products' preferences were significantly but only weakly correlated, indicating they represent different aspects of commercial preferences. Using our deep learning network, we could predict subjects' preferences with an average accuracy of 0.69.

Conclusions: To conclude, people's preferences seem to be influenced by relevant stimuli, such as commercials, while their liking and product value do not necessarily go hand in hand. Additionally, we show that our deep learning model can generalize to video commercials.

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A NOVEL TOOL FOR MEASURING THE CONTINUOUS CHANGES IN VALUE

Inbal Gur-Arie, *School of Psychological Sciences, Tel Aviv University*
Dino Levy, Sagol School of Neuroscience, Tel Aviv University and Coller School of Management, Tel Aviv University

Objectives: This study aimed to develop a tool for continuously measuring value changes during dynamic stimuli, such as video commercials, to capture moment-by-moment valuation shifts.

Methods: Subjects viewed 10 commercials (30-90 seconds) and continuously rated their liking on a 0-100 scale. Post-viewing, subjects rated overall liking and willingness to pay (WTP) on a 0-100 scale. Each video was viewed three times in a randomized order. Internal consistency was checked by correlating continuous liking scores across repeats, while validity was checked by correlating overall liking scores with average continuous liking.

Results: Subjects displayed high internal consistency in liking ratings($t(803) = 44.12$, $p < 0.0001$, Cohen's $d = 1.55$). Overall liking and average continuous liking showed a high correlation(average $r = 0.86$, $p < 0.001$). WTP and liking were moderately related(average $r = 0.47$). There was no agreement among subjects in dynamic(ICC = 0.01, $p = 0.85$) or averaged(ICC = -0.01, $p = 0.9$) likings, indicating variability in preferences. However, certain time points showed high agreement across subjects, identifying key factors within the commercials.

Conclusions: The tool reliably and validly measures continuous value changes during dynamic stimuli, enabling detailed tracking of neural correlates of value and identifying engaging segments within the stimuli.

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NEURAL ASYMMETRIC REPRESENTATIONS PREDICT THE DECOY EFFECT

Asaf Madar, *Sagol School of Neuroscience, Tel Aviv University*
Tom Zemer, Sagol School of Neuroscience, Tel Aviv University Ido, Tavor, Department of Anatomy and Anthropology, Faculty of Medical & Health Sciences, Tel Aviv University
Dino Levy, Coller School of Management, Tel Aviv University

Objective: The decoy effect is one of the most well-known effects in behavioral economics. Over the last 40 years studies have replicated the effect, focusing mainly on stimuli with explicit numerical properties. Nonetheless, they provide no tools when using real-world stimuli, as these stimuli lack numerical properties. Here, we propose a novel method for determining which stimuli would elicit the decoy effect, without using any of their explicit properties, based solely on the similarity of the neural representations of the stimuli as measured by functional magnetic resonance imaging (fMRI).

Methods: Subjects performed a Becker–DeGroot–Marschak task in the fMRI scanner (n=70), measuring their willingness to pay for participating in lotteries. We extracted the neural representation of each lottery for each subject. A different group of subjects performed a standard behavioral decoy effect task (n=133), choosing between sets of lotteries. We used the average neural similarity of the lotteries from the fMRI experiment to predict the magnitude of decoy effect in the behavioral experiment.

Results: We found significant predictions of the decoy effect (R^2_adj = 0.7086, p=0.0044) using neural representation similarities. Thus, we showed for the first time that the decoy effect can be predicted without relying on any stimulus explicit properties.

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Thalamo-cortical circuit dynamics underlying skilled performance of mice

Yoav Levy, *Department of Medical Neurobiology, Faculty of Medicine, Hebrew University of Jerusalem*
Ariel Gilad, Department of Medical Neurobiology, Faculty of Medicine, Hebrew University of Jerusalem

Objectives: To achieve higher-order cognitive functions, the brain engages a brain-wide network spanning multiple cortical and subcortical areas. Our research goal is to characterize the thalamo-cortical circuit dynamics by simultaneously observe multiple thalamic nuclei and cortical areas as mice perform different sensory discrimination tasks.

Methods: We first combine wide-field imaging and multi-fiber photometry to simultaneously image the whole dorsal cortex and 13 different thalamic nuclei of mice expressing genetically encoded calcium indicators. Mice are imaged during skilled performance of two different behavioral tasks; tactile and auditory discrimination.

Results: We observed significant increase in cortical activity during tactile tasks in comparison to auditory tasks. Interestingly, this increase appeared on Hit trials (when mice acted appropriately) but not on correct rejection trials (CR, when mice avoided action appropriately). Thalamic activity differed significantly between tasks as well; some nuclei responded in a similar activation or inhibition patterns across modalities, and some displayed significantly different responses.

Conclusions: Interestingly, some higher-order thalamic nuclei and cortical areas responded in a similar way for Hit or CR in both sensory modalities. Thus, we identified some critical hubs and dynamics that may underly choice. Our unique experimental system may aid in understanding the wide complexity of thalamocortical interactions.

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QUICK MINDS: INVESTIGATING THE ACCELERATION OF NEURAL PROCESSES IN AUTISM

Vishnu Priya Sampath, Yarden Weiss, Nathaniel Zuk, Jaroslav Slobodskoy-Plusnin, Aviel Sulem & Merav Ahissar

Edmond and Lily Safra Center for Brain Sciences, Hebrew University of Jerusalem

Objectives: Besides social challenges, autism is characterized by sensory atypicality, which shows that individuals with autism process sensory information differently than neurotypical individuals. Individuals with autism struggle in dynamic environments that require rapid adjustments based on ongoing events. We asked whether autistics have difficulties in adapting to fast changes when these changes are fully predictable.

Methods: We administered tones in short blocks, each with a fixed inter-stimulus interval (ISI). Blocks had either 500ms, 1000ms, or 1500ms ISIs, and were presented in a cluster. Consequently, participants could predict the coming block. To assess adaptation, we recorded EEG in Neurotypical (NT) adults (n=26), and people with Autism Spectrum Disorder (ASD) (n=25). To ensure alertness, participants performed an oddball task.

Results: Comparing the response to each block's first and second tones, we found a significant adaptation ($p<0.05$) in both groups, indicating the prediction of the first interval based on previous blocks. These results suggest homogeneous temporal processing in ASD, and NT participants displaying more consistent neural responses across different ISIs.

Conclusions: These findings indicate that people with ASD can adapt quickly when the dynamics are fully predictable. Keywords: Neural Dynamics, Autism, Temporal Predictions, Sensory Processing, Top-down, Adaptation

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Visual-Based Collective-Motion: The Key Visual Attributes Affecting Desert Locust Marching

Itay Bleichman - *School of Zoology, Tel Aviv University Peleg Shefi - Computer Science Department, Bar-Ilan university*

Gal A. Kaminka- Computer Science Department, Bar-Ilan university Amir Ayali - School of Zoology and Sagol School of Neuroscience, Tel Aviv University

Information extraction and processing is crucial for collective-motion-related decision-making, where the individual attempts to synchronize its movements while in noisy and cluttered visual surroundings. Various information-processing strategies can be employed, differing in their levels of complexity and computational demands. We investigated the tentative role of optic flow— the deformation of the image subtending the retina —in desert locust swarming. An alternative second visual attribute tested is that of the number moving objects in the visual field. Using a well-established experimental setup, we presented carefully controlled visual- motion stimuli to individual locust nymphs during tethered walking. Their behavioral response was later analyzed by means of precise video-tracking. We explored the nymphs' behavioral responses to different attributes of swarming related visual stimuli: the number of discrete objects; the total pixel area; and the total pixels in the moving edge. Our findings suggest that the swarming-related behavioral response is determined by an interplay between the number of objects and the moving-edge pixels, while the total pixel area does not affect the response. Our results shed light on the cognitive mechanisms underlying efficient information processing in complex and rapidly changing environments, a key aspect of animal collective motion.

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THE ORBITOFRONTAL CORTEX CONTRIBUTES TO LATENT STATE INFERENCE AND CONTEXT ADAPTATION IN MICE

Haneen Rajabi, Gabrielle Marmur, John Schwarcz, Robert Reiner, Eran Lottem

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Surviving uncertainty and inferring hidden features of the environment is a fundamental challenge for all organisms. To study the neural mechanisms that support such capacity we developed a novel auditory change detection task in which head-fixed mice were exposed to a random sequence of beeps in two hidden states: 'Unsafe' and 'Safe.' Transitions between states were un-cued, and licking was rewarded solely in the 'Safe' state, characterized by consecutive beeps. Uncertainty was manipulated by varying beep probabilities in the 'Unsafe' state. We assessed behavioral data (n = 15) and used a combination of pharmacological manipulations and electrophysiological recordings from the orbitofrontal cortex (OFC), a brain region thought to be important for latent state inference and flexible decision-making. Behavioral data revealed that mice adapted their response times based on the level of uncertainty, waiting longer when the probability of misleading beeps was higher. Moreover, we found that muscimol (GABA-A agonist) infusions to the OFC led to a marked deficit in the mice's ability to adapt to changing contexts (n = 9). Furthermore, a significant fraction of OFC neurons represented context. These results demonstrate an important role for OFC in cognitive inference and flexibility.

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Toward investigation of the neural basis of social decision-making

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Social decision-making is a complex process essential for societies and individuals across species, requiring choices within a social context while anticipating others' intentions and actions. While certain brain regions such as the midbrain and frontal cortex have been implicated in this process, how activity patterns within and across regions interact to underlie social decision-making remains unclear. To investigate the neural basis of social decision-making, we have established an experimental paradigm where mice can play a version of the iterated prisoner's dilemma game. In this model, two mice play one against another and make a decision each round. Following the decisions, the mice receive water rewards corresponding to the payoff resulting from the combined choices of the mice. Thus, the mice are required to make decisions contingent upon the collective strategies of both themselves and their conspecifics. Our setup enables mice to play either against a virtual strategy or against another mouse, and to either have or not have visual communication between the mice. It is compatible with all forms of neural recordings for freely moving mice, including multielectrode arrays and miniaturised microscopes. Thus, we aim to create a flexible platform for exploring the neural foundation of social decision-making.

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The effects of feedback on visual and vestibular heading discrimination

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We investigated the impact of feedback on vestibular and visual self-motion heading discrimination. We hypothesized: a) feedback for incorrect choices would increase 'choice-switching' (repulsion away from the previous choice), b) feedback for correct choices would increase 'confirmation-bias' (attraction to the previous choice), c) a positive relationship between effect of previous choices (without feedback) and the extent of an individual's autism spectrum traits (AQ). Participants (N=70) performed a heading discrimination task (with/without feedback), reporting whether a vestibular or visual self-motion stimulus was to the right or left of straight ahead. Fitting the data with a generalized linear mixed-effects model revealed that incorrect feedback significantly increased choice-switching compared to no-feedback ($p<0.0001$ for both modalities). However, feedback for correct choices didn't significantly increase confirmation-bias compared to no-feedback. The similarity in confirmation-bias with 'no-feedback' and 'correct-feedback' suggests that humans may, by default, assume that their choices are correct. Thus, feedback on incorrect choices may have a greater effect on perception or decision-making strategies. A positive relationship was seen between AQ scores and the effect of previous choices in the no-feedback vestibular condition ($r=0.35$, $p=0.0044$), suggesting increased confirmation bias in individuals with higher autistic traits. However, this effect wasn't observed in the visual condition ($p=0.65$).

Topic 3

Cognition : Language

Differentiating Reading Gains in Children with ADHD and Children with Reading Difficulties Using fMRI Data

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Introduction: Reading Difficulty (RD) is highly comorbid with attention-deficit/hyperactivity disorder (ADHD). Children with comorbidity of RD+ADHD demonstrate greater challenges in reading and executive functions (EF) compared to those with RD-only.

Objectives: To determine the effect of EF-based reading intervention on behavioral and neurobiological correlates for EF among 8-12 y.o. English-speaking children with RD+ADHD (n=19), RD-only (n=18) and typically developing children (n=18).

Methods: Behavioral and resting state fMRI data were collected before and after eight weeks of the EF-based reading computerized program. Functional connectivity matrices within and between EF networks were defined and compared between the participants. Prediction models connecting behavioral and neurobiological changes were conducted.

Results: All three groups improved in their reading and EF scores; however, children with RD+ADHD showed significantly greater improvement compared to children with RD-only. Furthermore, greater changes in functional connectivity post-intervention, mainly between FP and DAN, were found among children with RD+ADHD and RD-only, with significantly decreased functional connectivity of FP-DAN in the RD+ADHD group. Changes in FP-DAN significantly predicted increased naming abilities following training.

Conclusions: Results strengthen the role of EF in the reading process. Differential response to intervention was observed among these groups, which may bring the field closer to a precision-education approach.

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Neural Tracking of Acoustic and Linguistic Features of Spoken Hebrew

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Understanding how the brain processes speech remains one of the most important challenges of cognitive neuroscience. Although many studies have shown that neural responses in auditory cortex and language regions “track” the changes in speech envelope over time, less is known about the neural representation of phonetic, lexical and semantic features of continuous speech. Here we used a hierarchical multivariate approach to tease apart the contribution of acoustic and linguistic features to neural activity recorded while listening to continuous Hebrew speech. 27 adults listened to 60 Hebrew narratives, and answered questions about their content, as their neural activity was recorded using electroencephalography (EEG). We annotated the speech narratives in a precise time-resolved manner, to extract several linguistic features, including phoneme and word onsets, prosodic inflections, and semantic probabilities. Annotations were used to analyze the EEG response to speech, using multivariate linear reversed-correlation model, and we assessed the relative contribution of each feature to the measured neural response. In line with studies in other languages, we found that including linguistic features improved model performance relative to using acoustic features alone. This work lays the methodological foundation for understanding how the brain transforms speech-sounds into meaning during continuous Hebrew speech comprehension.

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What Triggers Task Conflict? Evidence From The Stroop Task

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When performing the color-word Stroop task, two main types of conflicts are activated: information conflict, which is the conflict between the incongruent word and font color (measured by the difference in reaction time for incongruent and neutral word conditions); and task conflict, which is the conflict between the contextually relevant color-naming task and the irrelevant, but automatic, word reading task (measured by the difference in reaction time for word and non-word conditions). In the present work, we focused on the conditions in which task conflict is triggered. Specifically, we tested whether and to what extent non-word conditions trigger task conflict (Experiment 1), and in which context task conflict is most strongly triggered (Experiment 2). Additionally, we examined how the saliency of the irrelevant task of reading increases task conflict (Experiments 3 and 4), and the role of response type (manual vs vocal response) in triggering it (Experiment 5). Our results provide evidence for the behavioral manifestation of task conflict and demonstrate the technical and theoretical properties of this mechanism, which is typically neglected in the Stroop task.

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GREATER BRAIN-TO-BRAIN SYNCHRONIZATION DURING STORYTELLING IN SPOKEN VS LITERARY ARABIC: AN EEG STUDY

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Introduction: One of the unique linguistic characteristics of Arabic is diglossia, which refers to the existence of two distinct forms of the same language: Spoken Arabic (SA), and Literary Arabic (LA). The level of familiarity with LA (vs SA) in children pre-reading age is important for their reading acquisition in school. However, a neurobiological marker for this different cognitive processing between SA and LA in pre-readers is still lacking. This study aims to examine the differences in joint attention to SA vs LA in pre-reading Arabic-speaking children using the Hyperscanning method, which enables simultaneous measurement of brain activity in two individuals.

Methods: Twenty-nine Arabic-speaking mother-child dyads (children's average age: 5.1 years, SD=0.789, 17 girls) participated in two 5-min dialogic reading conditions: SA and LA. EEG data was recorded simultaneously from the parent and the child (i.e. hyperscanning method), using a 64-channel EEG system (Brain Products, Germany, Ltd). Correlation coefficient matrices for brain-to-brain synchronization were conducted and compared between conditions using fisher-z transformation. Behavioral measures, including language abilities and nonverbal skills, were also collected.

Results: Greater correlation values between mother-child electrodes were found in the correlation coefficient matrix for the SA compared to the LA condition. In addition, a higher number of synchronized electrodes were associated with the SA condition. Moreover, a significant positive correlation was observed between the differences in vocabulary levels and listening comprehension between the LA and SA conditions ($r=0.5$, $p=0.02$).

Conclusion: These results offer neurobiological evidence for reduced joint attention in pre-reading Arabic-speaking children when exposed to LA compared to SA. Additionally, a greater difference in LA and SA vocabulary levels is linked to a larger difference in LA and SA listening comprehension. Future research should explore the impact of reading-based interventions on reducing the gaps in brain-to-brain synchronization between these two conditions.

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Topic 4

Cognition : Value representation

Revealing Neural Mechanisms of Learning from Positive and Negative Feedback Using Deep Reinforcement

Tamir Scherf, *WIS Kristoffer C., Aberg , WIS*
Tamar, Reitich-Stolero, WIS Rony, Pas WIS

Deep Reinforcement Learning (Deep RL) opens exciting opportunities for modeling of brain and behavior. In our study we utilize recent advancement in the use of Deep RL in neuroscience to reveal basic computational mechanisms of learning. We use an actor-critic model with a variation of fMRI encoding analysis to examine brain activations in a restless three-armed bandit task. By exploring the network's activations, we found separate units in the model that represent standardized positive and negative feedback. Interestingly, these representations were more prominently coded in different brain regions, implying distinct neural representations. Our results emphasize the importance of examining basic properties of behavioral models to explore the neurocomputational mechanisms of behavior.

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THE ROLE OF THE CEREBELLUM IN FLUID INTELLIGENCE: AN FMRI STUDY

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Traditionally, neuroimaging studies on fluid intelligence have focused on brain activation in frontal-parietal regions. In the past decade there has been accumulating evidence regarding the involvement of the cerebellum in higher cognitive function. This study aimed to further investigate the role of the cerebellum in processing of fluid intelligence. Thirty-nine participants were scanned while performing a novel abstract reasoning fMRI task, modeled after stimuli from the advanced Raven's Progressive Matrices test. Analyses of both brain function and network architecture were performed. Our analysis yielded 12 significant clusters illustrating a broad fronto-parietal network activation including the inferior and middle frontal gyrus, inferior and superior parietal lobule, inferior occipital lobe and the supplementary motor area. Also, we found activation in cerebellar regions: bilateral cerebellum IX, right cerebellum crus I and right cerebellum VII. Moreover, four cerebellar regions and the middle and inferior temporal gyri, the cingulate gyrus and the thalamus served as hub regions. We demonstrate activation in frontal and parietal well-known regions, together with an extensive activation in several cerebellar sub-regions, which also served as crucial hub regions. We provide evidence of the role of the cerebellum in fluid intelligence by means of task brain activation and graph theory topology.

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Orbitofrontal cortex projections mediate neuronal probability estimation in the piriform cortex

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Rafi Haddad, The Multidisciplinary Brain Research Center, Bar-Ilan University

Estimating the statistics of events occurring around us is a crucial feature for survival. However, how the brain encodes and updates these internal probability distributions and at what processing level is poorly understood. Here, we devised an odor-discrimination task where mice could utilize preceding odor cues to estimate the probability of encountering a subsequent odor. Recording the neural activity in the primary olfactory cortex along the learning process, we found two non-overlapping neuronal subpopulations that encode the odor probability contingencies differentially. One subpopulation exhibited informative activity on the probability of the upcoming odor before it arrived. The second subpopulation signaled the stimulus prediction error when it arrived. Bilaterally silencing the orbitofrontal cortex (OFC) before or after learning hampered mice's ability to utilize the cue-probability contingencies and eliminated its neuronal coding in the Piriform cortex. However, it did not affect the prediction error signals. These findings suggest that neural activity in sensory cortex contains information on its probability and reveals that OFC is necessary for probability coding but not for generating prediction error signals.

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Priming whole-oriented vs. detail-oriented processing transfers across different tasks and sensory modalities

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Global-local processing framework has garnered significant attention in cognitive psychology, sparking debates regarding its existence and implications. While some cognitive and clinical studies suggest the existence of a global-local system, recent investigations have raised questions about its validity. This study aimed to investigate one crucial aspect of this question – the transferability of primed global or local processing styles across different tasks and modalities. For that aim, 80 participants were randomly assigned to a global or local priming group, using a visuospatial Navon-like task. Subsequently, they completed tasks assessing global-local processing tendencies in (a) a visuospatial task similar to the priming task, (b) a visuospatial task different from the priming task, and (c) an auditory task. The results yielded a significant transfer effect of global-local processing tendencies across all tasks and modalities, with priming influencing subsequent processing styles. These findings support the existence of a general global-local system. Furthermore, they provide initial evidence that this system can be influenced. These results are consisted with some previous studies but not with others, highlighting the differences in the definition of the global-local system as a potential cause for discrepancies. These findings have potential implications for various psychological aspects related to mental health.

Topic 5

Cortical and hippocampal circuits in Navigation

Auditory representations of place and identity for others in the primate hippocampus

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For almost half a century, the mammalian hippocampus was known to form representations for self. This dogma is starting to change with recent findings of hippocampal representations of others. While these social-spatiotemporal representations rely mostly on vision, a key component of social behavior in mammals is vocal communication. However, it is unknown if the hippocampus encodes auditory social-spatial representations during vocal communication. Here we investigated whether neurons in the marmoset hippocampus encode the location and identity of conspecifics by a unique social communication call – phee-calls. Phee-calls are used by marmosets to exchange self-spatial information between conspecifics in the absence of visual sight. We recorded neurons across the hippocampal dorsal-ventral axis, while monkeys engaged in phee-calls communication with a closed-loop playback system. To this end, we used a database of 47,672 labeled phee-calls to manipulate the location and identity of the conspecific. Our preliminary results revealed hippocampal cells tuned for self-position (classic place-cells), as well as cells tuned for calls produced by self, and cells tuned to calls produced by others, and encode position × identity. Our findings reveal, for the first time, auditory representations for place and identity, and for self and others in the primate hippocampus.

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Neurobiology of navigation in the real world: Hippocampal spatial codes in bats navigating outdoors on a remote oceanic

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Shaked Palgi, Weizmann Institute of Science
Shir Maimon, Weizmann Institute of Science
Tamir Eliav, Weizmann Institute of Science
Avishag Tuval, Weizmann Institute of Science
Chen Cohen, Weizmann Institute of Science
Liora Las, Weizmann Institute of Science
Nachum Ulanovsky, Weizmann Institute of Science

Our understanding of how the brain represents the world stems from experiments in constrained laboratory settings that investigate what the brain can encode, but leave the fundamental question unexplored – how does the brain actually represent the real world? We tackled this challenge by performing the first single-unit neural recordings outdoors from freely navigating bats on a remote oceanic island. We developed a wireless neural-logger with an integrated high-precision GPS and altimeter – and recorded electrophysiological activity from hundreds of single neurons in the dorsal CA1 region of the bat's hippocampus, together with the bat's position and altitude in the real world. We found that as the bats navigated the island, hippocampal neurons exhibited place fields in three-dimensions (3D), with single place cells having multiple place-fields in 3D. The unconstrained bats flew at different altitudes over the island, and preliminary results indicate that different place-fields of single neurons encode distinct altitudes. Here we will describe these and other findings from a large dataset that we recently recorded from bats flying outdoors – providing the first view on spatial coding in the mammalian hippocampus during real-world navigation.

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Neurobiology of navigation in the real world: Head-direction cells serve as a neural compass in bats navigating outdoors

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Department of Brain Sciences, Weizmann Institute of Science

Navigation is crucial for animals and humans. Historically, studies of navigation were either conducted by ecologists tracking animals in real-world environments, or by neuroscientists recording neural activity from animals navigating indoors in small laboratory enclosures. To bridge the gap between these two approaches, we conducted the first study of neurons in the brain's "navigation circuit" during outdoors navigation. We focused on head-direction cells, which represent the animal's orientation. To this day, no study tested if head-direction cells exist outdoors – and if they do: Do they function as local compasses, which remap between environments, or as global compasses, which maintain a stable representation over time and space. To this end, we developed wireless electrophysiology and high-accuracy positional tracking, and recorded hundreds of single neurons in the presubiculum – a key hub of head-direction cells – while bats were flying and navigating outdoors on a remote oceanic island. We found head-direction cells, which encoded orientation globally: They showed stable directional tuning over the island's geographical space, and maintained the same preferred direction regardless of appearance, disappearance, or rotation of the moon. Together, our results suggest that head-direction cells can serve as a neural compass during real-world navigation outdoors.

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Simultaneous calcium and voltage Imaging in excitatory and inhibitory neurons in the mouse hippocampus

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ShulamIt Baror-Sebban (ELSC), and Yoav Adam (ELSC)

Two-photon Calcium imaging is a popular technique to study neuronal activity in behaving animals. While somatic calcium dynamics are considered a proxy for spiking activity, little evidence directly supports this assumption. We developed a bicistronic viral construct for co-expression of the voltage indicator Archon1 and the calcium indicator GCaMP8m. We also developed an imaging system allowing simultaneous high-speed voltage imaging and 2-photon calcium imaging. Using this toolkit we systematically compared the calcium dynamics to the ground-truth voltage signals of pyramidal cells (PCs) and interneurons (INs) in the mouse CA1. Our data revealed that calcium transients in PCs are linearly related to the firing rate (FR) in cases of regular spiking but diverge from linearity during complex spike events. INs show high firing rates which often result in no apparent calcium activity. Carefully examining the voltage-to-calcium transformation in INs occasionally showed a positive correlation of the calcium with the FR while other cells displayed negative or no correlation. Overall, our data call for careful interpretation of calcium imaging data, particularly in the case of INs. Furthermore, calcium is a key signal for learning and plasticity. The experimental approach we developed will allow detailed mechanistic studies of calcium-voltage dynamics during learning.

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MULTI-MODULE GRID CELLS IN THE MEDIAL ENTORHINAL CORTEX

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Grid cells in the medial entorhinal cortex are functionally organized in subgroups (called grid modules), each characterized by a distinct spatial scale. Population analysis of individual grid modules has shown that each module internally represents a latent two-dimensional variable, manifested in the position of the joint activity on a manifold with toroidal topology. It is unknown, however, whether there are mechanisms that link the activity in different modules. We used simultaneous recordings from thousands of entorhinal cells to investigate the tuning of individual cells to the internally represented latent variables. We developed a method to identify the toroidal tuning of each cell, and to subsequently decode the dynamics of the latent variables based on the neural recordings. Surprisingly, we next identified previously unknown sub-populations of neurons that are sharply tuned to two modules, a phenomenon we refer to as ‘co-tuning’. This property of the cells is manifested in their spatial firing patterns, which could otherwise be misinterpreted as a distorted grid pattern. Intriguingly, co-tuned cells are predominantly observed in modules with consecutive grid spacings and are anatomically distributed near the boundary between the two modules. We speculate that the co-tuned cells may be involved in an interaction between grid modules.

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Context dependent Spatial Representations in the Hippocampus

Daniel Zur, Hadas Benisty, Dori Derdikman

Technion

The hippocampus is essential for learning and memory, particularly in spatial and temporal processing, contributing to the brain's cognitive map. Our research investigates these spatial representations by recording neuronal signals from freely moving mice using a probe. In our setup, mice explore a two-room arena in a structured sequence: 20 minutes in Room A, 20 minutes in Room B, and a final 20 minutes back in Room A. Our aim therefore is to explore the way each room is represented, in a search for intrinsic features that are remapped across different rooms (contexts) as opposed to features that are being preserved. To quantify the similarity in spatial representation across rooms we trained a series of models for the prediction of location based on hippocampal firing rate. We used regularized linear models to identify which sub-populations participated most in the encoding of spatial information. Additionally, we used Gated Recurrent Units (GRUs) to capture temporal dependencies and non-linearities. Our results show that the hippocampal network encoding of allocentric location is remapped when transitioning to a different room (A to B) while being preserved during a second visit to the same room (A to A).

Topic 6

Development: : Development of Motor, Sensory, and Limbic Systems

MECHANISMS INVOLVED IN THE DEVELOPMENT OF SENSORIMOTOR SYNCHRONIZATION SKILLS

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Gal Vishne, The Hebrew University, Jerusalem, Israel Merav Ahissar, The Hebrew University, Jerusalem, Israel

Objectives: This study aims to characterize computationally the developmental trajectory of sensorimotor skills.

Methods: 198 children ages 5-13 and 39 adults completed a 3-minute-long paced finger tapping task consisting of 3 blocks. In the first two blocks, participants synchronized their taps to a fixed metronome beat of 400 or 500ms. In the third block they synchronized to a tempo which alternated between 500ms and 400ms every 6-8 seconds.

Results: Children's synchronization skills (as indicated by variability around mean error) improved with age, but did not reach adult level. A step-by-step computational model revealed that children's ability to correct local asynchronies (errors) was like adults. Their bottleneck was due to reduced reliability in retaining intervals in short-term-memory, this enhanced noise limited their ability to track tempo changes. With mild noise elevation they tracked changes slowly. With larger noise levels, they "re-started" synchronization upon tempo changes.

Discussion: We conclude that the main limiting factor to children's synchronization is elevated working memory noise.

Topic 7

Disease models

Can zebrafish scuba dive? The effect of hyperbaric oxygen on the brain

Daniel Forer (Israel)1; Ayelet Hallakoun (Israel)1 ; Ricarina Rabinovitz (Israel)1 ; Yehuda Arieli (Israel)2 ; Tali Lerer-Goldshtein (Israel)1 ; Lior Appelbaum (Israel)1

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Cellular respiration is crucial for energy production in organisms, relying on oxygen (O2). However, exposure to high oxygen partial pressures (PO2) can lead to a fatal neurological condition known as central nervous system oxygen toxicity (CNS-OT). Despite the risk, hyperbaric oxygen (HBO) is used in medical and diving applications. To understand its effect on brain function, we used a custom-made mini pressure chamber and live imaging in transparent zebrafish. The zebrafish CNS has a highly functional, physiological, and genetic homology with that of mammals. Around 70% of human disease-causing genes have functional homologous in zebrafish, making them useful for studying genetics and neuronal development. The study in zebrafish confirmed findings from rodents and humans, showing altered gene expression under HBO, including markers for hypoxia and oxidative stress. Heart rate also decreased in response to HBO. Using behavior tracking and imaging, we observed seizure-like brain activity and behavioral changes under HBO. By imaging the blood-brain barrier (BBB) in live zebrafish, we detected changes in blood diffusion rates, suggesting BBB leakage as a contributing factor to CNS-OT during HBO exposure. These findings shed light on the neurological effects of high oxygen levels and the potential risks associated with HBO treatment.

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A new rat model for retinal degeneration: The GCaMP6f+\- RCS-\- Rat

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Retinal degeneration (RD) is one of the most common causes of blindness in the western world. Our research aims at developing an animal model which can significantly enhance the functional evaluation of treatment modalities aimed at vision restoration in these patients. The development of the novel rat model is based on a new breed in which Royal College of Surgeons (RCS) rats, a well-known model with RD, is crossbred with the transgenic line LE-Tg(Thy1-GCaMP6f)7, which expresses the genetic calcium indicator GCaMP6f. Characterization of the novel model was obtained using OCT imaging, ERG recording and histology. , Moreover, ex-vivo electrical stimulations were performed, using Multi-Electrode Array. Our results revealed the RD expected in the RCS breed accompanied by the fluorescent RGCs, this was observed in both OCT imaging and histological studies. B-wave component was observed up to 8 weeks (albeit weak). In addition, subretinal electrical stimulation demonstrated the feasibility of the investigation of activation thresholds and the building of strength duration curves. Interestingly, in the investigated age groups (up to 12 weeks) no significant change in the activation threshold was observed. This developed breed will prove to be a vital tool in the investigation of the efficacy of vision restoration strategies.

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Site specific RNA editing as a therapeutic approach for STXBP1-Encephalopathy

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Syntaxin binding protein 1 (STXBP1) plays a key role in docking and fusion of presynaptic vesicles. Inactivating mutations in STXBP1 lead to STXBP1-Encephalopathy (STXBP1-E), a neurodevelopmental disorder for which there is currently no efficient treatment. R406H, a highly recurrent de novo pathogenic mutations, leads to STXBP1-E. Adenosine (A) to inosine (I) RNA editing, catalyzed by adenosine deaminases acting on RNA (ADAR) enzymes, offers a mean to specifically correct guanine (G) to A mutations as the cellular translational machinery recognizes I as G. Thus, we aim to assess ADAR enzyme RNA editing as a potential treatment for STXBP1-E patients carrying the c.1217G>A R406H mutation. We generated and fully characterized iPSCs from a patient carrying R406H mutation and from its healthy sibling as control. We validated that the mutation is present both at the DNA and RNA of the cells generated from the patient. Moreover, microelectrode array analysis demonstrated differences in electrophysiological activity between cortical neurons derived from the patient in comparison to its control. We further intend to apply molecular and biochemical methods to establish other phenotypes associated with STXBP1-E. We will then attend to recruit ADAR by overexpression of a specific guide and test its ability to rescue these phenotypes.

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A new Therapeutic Approach for Smith Magenis Syndrome using Retinoic Acid derivatives

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Smith-Magenis Syndrome (SMS) is a rare neurodevelopmental disorder characterized by intellectual disability, autistic-like behaviors, behavioral problems, sleep disturbances, distinctive facial features, and physical and developmental abnormalities. SMS is typically caused by an interstitial 17p11.2 deletion involving the RAI1 gene (Retinoic Acid Induced 1) or a mutation in RAI1. Molecular and clinical evidence has identified RAI1 as the causative gene for SMS, while the variable features and severity of symptoms can be influenced by other genes located on chromosome 17p11.2. To this day, SMS has no cure. and treatment focuses on managing symptoms and providing support. Retinoic acid (RA), a derivative of vitamin A, regulates the expression of the RAI1 gene. Within the promoter region of the RAI1 gene, specific sequences known as retinoic acid-responsive elements (RAREs) are present. When RA binds to the retinoic acid nuclear receptor (RAR), it becomes activated. Subsequently, the activated RA-RAR complex interacts with RAREs, thereby modulating the expression of the RAI1 gene This study proposes a novel treatment approach for SMS involving RA derivatives. We plan to utilize hippocampal neurons derived from SMS patients, treat them with RA, and conduct periodic clinical assessments of SMS patients undergoing RA treatment in collaboration with Rambam Hospital.

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Exploring MeCP2's Role in DNA Damage Repair and Its Implications for Rett Syndrome

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Rett Syndrome (RTT) is a neurodevelopmental disorder characterized by an apparently normal early development followed by significant developmental regression. Affected individuals experience a loss of speech and motor skills, exhibit autism-like features, and often suffer from respiratory complications, epilepsy, anxiety, and orthopedic issues. Almost all cases of RTT are caused by loss-of-function mutations in the methyl CpG binding protein 2 (MeCP2) gene. Extensive research has aimed to elucidate the complex roles of MeCP2, with a predominant theory suggesting that MeCP2 acts as a transcriptional repressor via its methyl binding domain (MBD) and transcriptional repression domain (TRD). Additionally, MeCP2 undergoes activity-dependent phosphorylation, which suggests a dynamic function in the brain. Despite significant progress, the pathophysiology underlying RTT remains incompletely understood. Recent evidence showing an interaction between MeCP2 and Topoisomerase II beta (TOP2B), an enzyme involved in the repair of DNA double-strand breaks, suggests a novel role for MeCP2 in DNA damage repair. This hypothesis aligns with the hallmark feature of RTT, developmental regression, and may also explain the protein's phosphorylation dynamics, which could be crucial in recruiting repair complexes. In our study, we utilized immunohistochemical staining of γ-H2AX, a DNA break marker, to quantify accumulated DNA damage in RTT model cells. We demonstrated that both baseline and induced DNA damage levels are higher in RTT models compared to controls. We are currently optimizing and engineering novel biosensors to allow dynamic visualization of DNA damage in the nervous system. Our findings and future work will illuminate a previously unrecognized role of MeCP2 as a regulator of DNA damage repair, offering new insights into the pathophysiology of Rett Syndrome.

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Exosomes can modulate the early hyperexcitability in cortical neurons with ASD-associated Shank3 mutation

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Shank3, a scaffolding protein, is critical for synaptic structure and function, particularly in the formation and maintenance of dendritic spines. Shank3 mutations are strongly implicated in autism spectrum disorder (ASD) and related neuropsychiatric conditions such as Phelan-McDermid Syndrome (PMS) a.k.a. 22q13.3 deletion syndrome. Previous work, including our study, has demonstrated that mutations in ASD-associated genes exhibit early hyperexcitability as a potential common endophenotype. Moving forward, in this study, we have performed a neurophysiological analysis of Shank3 (c.3679insG mutation) induced pluripotent stem cell (iPSC)-derived cortical neurons to gain insights into the pathophysiology of ASD. First, utilizing exosome-based intercellular communication, we sought to understand the implications on the neurophysiology of Shank3 mutant and control

neurons after exosome switching. We found that while control neuron-derived exosomes do not change the neurophysiology of Shank3 neurons, however, the Shank3 neuron-derived exosomes could transfer the early hyperexcitability to control neurons via exosomes. Next, we also explored the therapeutic potential of mesenchymal stem cells (MSC) and iPSC-derived exosomes from healthy donors in the Shank3 iPSC model of ASD. We demonstrate that both MSC and iPSC-derived exosomes could rescue the early hyperexcitability in Shank3 neurons. Proteomic analysis of exosomes derived from Shank3 mutant and control neurons, as well as from MSC-exosomes and iPSC-exosomes, revealed distinct protein cargoes that could influence the neurophysiological properties of recipient cells. Our results provide novel insights into the pathophysiology of ASD emphasizing the importance of exosomes in intercellular communication and their potential to influence neuronal activity in the human central nervous system (CNS). Moreover, our findings support the need for further exploration of exosome-based interventions as potential therapeutics for treating neurodevelopmental disorders.

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Brain-wide neuronal network in Autism-like mice model compared to WT mice

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Studying neuronal networks is essential for understanding different brain processes and can provide insights into the underlying mechanisms governing cognition, behaviour, emotions, and neurological disorders. Moreover, understanding neuronal networks in a healthy brain versus an unhealthy brain can lead to a higher understanding of various brain disorders. In our research, we use calcium imaging to compare brain activity in WT versus autism-like mice model to detect brain activity in various brain areas simultaneously. To achieve this, we insert optic fibres into multiple brain areas known to play a role in high cognitive and emotional processes. Using this multifiber photometry system, we can track brain-wide neuronal dynamic as mice preform several freely moving behavioral tasks, including anxiety tasks (elevated plus maze and open field), social task (3-chamber task) and memory task (novel object recognition). Our hypothesis is that neuronal networks in the Autism-like mouse model differ from those of WT mice, especially in emotional-related areas such as the amygdala. Our results outline significant differences in brain-wide network patterns between WT and Autism-like models. These differences are linked to specific behavioral tasks and highlight the brain-wide dynamic dysfunction that may underline Autism.

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ELUCIDATING THE CELLULAR FUNCTIONS OF TIMM50, A MITOCHONDRIAL TRANSPORT PROTEIN, IN NEURONS AND ASTROCYTES

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Timm50, is an essential member of the Translocase of inner mitochondria membrane (TIM23) complex subunits. Therefore, defects in its function, are expected to lead to devastating cellular effects. Timm50 mutations have been linked to general neurodevelopmental defects. Until now, most studies were conducted with patient's fibroblasts. However, it is apparent that the common ground between the different phenotypes, is neurological in nature. Due to Timm50 known functions, the link between the mutations and neurological deficiencies is expected, but has not been fully characterized yet. We aim to generate Timm50 mutated hiPSC-derived cortical neurons and examine, for the first time, the pathological effects of Timm50 mutation in human brain cells. The analysis of the differentiated neurons will include examination of effects on cellular and mitochondrial proteome and metabolome and of neuronal activity using several methods including whole-cell patch-clamp, western

blot and immunofluorescence. First, we started to reprogram human fibroblasts, obtained from skin biopsies of two Timm50 patients and one healthy control and successfully managed to differentiate them into cortical neurons, using well-established methods. The results from this study will enable us to unravel the molecular basis of the Timm50 disease and in the long term probably to develop cure for it.

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The involvement of amygdala neurons in sex-specific social abnormalities of Pogz+/- mice

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De novo mutations in POGZ lead to intellectual disability and developmental delay, with features or diagnosis of ASD. We have performed behavioral assays on a Pogz+/- and control mice and found genotype-sex interactions across social and communication-related tests. In this study, we sought to identify the biological mechanisms underlying the sex-specific social abnormalities observed in the Pogz+/- mouse. Mice were exposed to a novel social odor, and their brains were labeled for the activation marker cFos. We found a significantly higher number of labeled neurons in the amygdala of Pogz+/- male mice. To achieve in-vivo high-resolution mapping of these activated neurons, we crossed our mice with TRAP2; Ai14 mice allowing us to permanently label the active cells during social recognition. Measuring the morphophysiological properties of the labeled neurons using in-vitro whole-cell recordings, we found four types of principal neurons, characterized by unique AHP and spike trains of action. To identify genes and neuronal populations which may underlie this behavior, we aim to perform SC-RNA sequencing on labeled and unlabeled neurons. Our preliminary results in this study, support a specific and significant sex-biased role of POGZ in regulating social behavior, influenced by circuits in the amygdala.

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Zebrafish model for the neurodevelopmental disorder iqsec2-deficiency

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Epilepsy is a chronic disorder that is characterized by recurrent unprovoked seizures. Mutations in IQSEC2 have been associated with X-linked nonsyndromic intellectual disability (ID), autism, and severe childhood epilepsy. IQSEC2 is a guanine nucleotide exchange factor for the small GTP-binding protein Arf6 that localizes to the postsynaptic density (PSD) of excitatory synapses. In the synapses, IQSEC2 form a protein complex with N-methyl-Daspartate-type glutamate receptors (NMDARs), possibly via a direct interaction with PSD-95 and insulin receptor. The disorder is studied in mammals and human cell lines, however, the neurological mechanism is unclear, and treatment is unavailable. We employed the zebrafish model to investigate IQSEC2-deficincy. Zebrafish is a transparent vertebrate, with evolutionary conserve genome and brain structure with mammals. We generated two transgenic zebrafish models that expresses wild type [tg(uas:EGFP-WThiqsec2)] and mutant [tg(uas:EGFP-Muthiqsec2)] human IQSEC2. Using live imaging of single neurons, and video tracking of behavior, we found altered neurological development and abnormal behavior in tg(uas:EGFP-Muthiqsec2). This zebrafish model will provide a platform to test potential drugs and genetic treatment for IQSEC2-deficincy.

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Developing a genetic treatment for GRIN2B disorders using transgenic mouse and rat models

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NMDA receptors (NMDARs) are glutamate-gated ion channels essential for neuronal communication and synaptic plasticity. These receptors are composed of two GluN1 subunits and two additional GluN2 (A-D) subunits. The receptor composition varies across different regions of the brain and changes throughout development and in response to neural activity. Mutations in NMDARs are strongly implicated in various neurological disorders, including intellectual disability, developmental delay, autism spectrum disorder, and epilepsy. Systematic screenings of pediatric patients have identified thousands of inherited or de novo mutations in the most abundant subunits in the brain, namely GRIN2A and GRIN2B. Our previous research has characterized two distinct GRIN2B mutations (p.G689C, p.G689S) and found that these mutations completely disrupt the subunits' ability to respond to normal glutamate levels, rendering the receptors inactive at the synapse. Given the lack of treatments for GRINopathies, this project aims to develop novel therapies for affected patients. We plan to restore functional subunits using viruses capable of crossing the blood-brain barrier (BBB) to achieve brain-wide expression of the wild-type GRIN2B subunit. We will test these viruses in two transgenic models: heterozygous GRIN2B G689C knock-in mice that we have produced and a heterozygous GRIN2B knockout rat model.

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ABERRANT DEVELOPMENT AND ECM DEPOSITION IN FRAGILE X BRAIN ORGANOIDS

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Fragile X syndrome (FXS) is the most common form of inherited intellectual disability and monogenic cause of autism spectrum disorders, caused by silencing of the FMR1 gene. Studies have shown that altered deposition of ECM proteins may play a significant role in FXS. For example, the ECM glycoprotein Tenascin-C has been shown to be upregulated in the brain of FMR1 knockout mice, and may relate to increased excitatory synapse formation and dendritic spine length. Additionally, high levels of matrix metalloproteinases (MMPs) and their over-activity have been shown to affect synaptic plasticity and memory formation in both drosophila and murine FXS models. Using a unique model of FX-human embryonic stem cells (FX-hESCs) and their isogenic controls we have demonstrated that brain organoids derived from FX-hESCs exhibit aberrant development and growth. This disparity may be overcome by using Wnt and TGFbeta inhibitors. Immunofluorescence and proteomic analyses revealed differential expression of neural markers. SOX2 and PAX6 were upregulated, while TUBB3 and DLG4 were downregulated in FX-organoids. Western blot and qRT-PCR revealed dysregulation of several ECM-related proteins in FX-organoids, and immunofluorescence analysis further uncovered altered deposition patterns of these proteins between FX- and IC-organoids. These findings suggest impaired differentiation and development in the FXS brain, implicating the ECM as having a pivotal role in FXS brain development.

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Topic 8

Learning and memory: Behavior

Uncoupling memory tasks from language: linking anticipatory gaze effects and explicit memory reports

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Asking a participant to report whether they remember is a high threshold that confounds the presence of episodic memory with its measurement, and neglects its presence in populations that may not be able to report (e.g. patients, infants, non-human primates). Put simply, memory can be present even when it is not verbally reported. Here, we developed a paradigm that tracks eye-movements to quantify the degree to which episodic memory is present. During repeated viewing of animations, participants (n=31) encoded and retrieved a surprising event in two sessions 2 hours apart. Gaze direction during the second viewing anticipated the surprising event. By comparing this gaze effect to explicit verbal reports, we found that anticipatory gaze correlates with reports of having seen the scene before. Moreover, gaze measures correlate with memory reports of the content of the event and its location. We are now investigating the underlying brain activity using a combination of fMRI and eye tracking. Overall, we demonstrate that this paradigm is able to reliably measure memory via an anticipatory gaze effect. Specifically, correlations with explicit reports regarding the event's content and location suggests that the anticipatory gaze effect can assist in measuring episodic memory in the absence of language.

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Frequency-dependent long-term de novo learning of continuous control

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Learning a new motor skill requires the formation of a completely new controller, a process termed as de novo learning. Initially, learning involves establishing arbitrary mappings between actions and outcomes. With practice, learning enables rapid and more efficient responses. However, the evolvement across time of such responses and their dependency on the speed of environmental changes (i.e., frequency) is still unclear. Here, we aim to explore frequency-dependent mechanisms involved in longitudinal de novo learning. We recruited 9 healthy participants (24.7±2.0 years) who learned a mirror reversal continuous tracking task, a well-accepted paradigm of de novo learning, over 5 days, with a target moving at various frequencies. Movement's trajectories were analyzed using discrete Fourier transform to identify frequency-dependent patterns. We found distinct frequency-dependent learning processes. While participants rapidly mastered the transformation at low frequencies, learning at high frequencies was initially limited. This reduced high-frequency learning, however, gradually evolved. This difference could be attributed to reliance on feedforward control at low frequencies, while high frequencies presented challenges due to reliance on inappropriate feedback responses. Nonetheless, the feedback controller gradually improved with practice. Our findings highlight the frequency-dependent nature of de novo learning, contributing to our understanding of acquiring real-world skills.

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Neural correlates of fast, few-shot learning in the orbitofrontal cortex of freely-moving rats

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When studying learning, significant heterogeneity in learning rates was observed across different tasks and environments. These can differ by factors of up to 10,000. Fast, few-shot learning on one end of this spectrum are particularly interesting. We implemented a novel behavioral task that tests learning and exploration strategies in freely-moving rats in an enriched and unrestrictive environment with self-initiated behavior, all features that were recently found to increase learning rates. To study the neural correlates of these behaviors, we record electrophysiological activity from the Orbitofrontal cortex (OFC) using high-count silicon electrodes (Neuropixels). Rats were able to learn the task very fast, reaching near-optimal performance with 1-3 reinforcements. Behavior was consistent across rats, with hierarchical learning and largely random exploration with some biases. There are strong hints that the rats applied model-based learning. OFC neurons showed robust responses with temporal patterns that were varied among neurons but occurred in all rats.

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Neuroplasticity-based parcellation of the brain - a continuous diffusion MRI study

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Learning-induced neuroplasticity involves structural and functional changes which can be detected after short learning periods by Magnetic Resonance Imaging (MRI) (Brodt et al., 2018; Tavor et al., 2020; Jacobacci et al., 2020). Here we explore how microstructural neuroplasticity during the learning process relate to brain connectivity, offering a neuroplasticity-based brain parcellation. To follow on continuous changes during learning, we developed a unique protocol of diffusion tensor imagining (DTI) (Basser et al., 1994). Fifty-eight right-handed healthy volunteers were scanned during a 40-minute finger-tapping task (Karni et al., 1995) or as a passive control. Using a sliding-window method, we calculated continuous mean diffusivity (MD) to create a 'microstructural time-series', reflecting the ongoing changes in tissue diffusivity during learning. Multiple gray matter motor-related regions displayed a significant decrese in MD while learning ($P < 0.05$, FDR-corrected). We than parcellated the brain into five 'neuroplasticity networks' based on similarities between different areas' change patterns. We further explored the similarities between these networks and canonical functional connectivity networks. This work offers a network-level perspective on brain connectivity by examining short-term training-induced microstructural changes. By clustering brain areas according to their plasticity patterns, we provide a new approach to studying brain connectivity and function while learning.

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Impacts of Direct and Indirect Fear Exposure on Memory and Intergenerational Trauma

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Objective: October 7th's surprise attack in Israel highlighted the impact of traumatic events on mental health. Studies indicate that unexpected chronic stress affects directly exposed rodents and their offspring across generations. Observational fear-learning (OFL) may induce similar physiological responses and brain regions' engagement as direct fear conditioning. Therefore, this study examines the behavioral, physiological, and genetic impacts of direct and indirect fear exposure on short-term and long-term fear memory and explores the transmission of trauma effects to subsequent generations, focusing on fear learning and anxiety-related behaviors in offspring.

Methods: Female rats were exposed to direct fear conditioning, indirect exposure (observing conspecifics in pain), minimal exposure (environmental context), and no exposure (control). Behavioral changes and gene expression were analyzed, along with offspring behavior and physiological responses.

Results: Preliminary findings indicate a difference in behavior between direct and indirect exposure to fear. Direct fear exposure had a significant impact on short-term memory. Ongoing experiments are under way to determine general anxiety adn social function following indirect fear learning.

Conclusions: This research enhances the understanding of fear memory mechanisms and the heritable nature of trauma-related behaviors. Future studies could further elucidate the molecular pathways involved in these processes.

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IMAGES THAT ARE MORE "FACE-LIKE" ARE BETTER REMEMBERED DURING NATURALISTIC ENCODING

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We have recently found that bigger images and higher-contrast images are better remembered during naturalistic encoding. In these studies, we have also found that human faces were best remembered from the categories tested. Face pareidolia is the phenomenon of spontaneously perceiving illusory faces in inanimate objects/scenes. Here we assumed that since face pareidolia images activate both face- and non-face processing networks they will be remembered better than their control (non face-like) images during naturalistic encoding. In a set of 4 online experiments (n=188) we consistently found that during naturalistic encoding face pareidolia images were remembered more than their control images and interestingly also more than human face images. We also found that faceness ratings predicted memory such that images rated as more face-like were remembered better than images rated as less face-like. While image memorability scores (based on participants' performance) reflected the memory results, ResMem, a dedicated artificial neural network (ANN) trained to estimate image memorability, did not capture the memorability difference between face pareidolia images and their control images. These results highlight the complexity of human visual representations and further suggest that human memory during naturalistic encoding may indirectly indicate the extent of activity elicited during image encoding.

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IMAGE MEMORY DURING NATURALISTIC ENCODING IS NOT ADVERSELY AFFECTED BY AGE IN ADEPT PARTICIPANTS

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Not much is known about visual memory during naturalistic visual behavior, and this may be critical during aging as aging-vision is associated with multiple changes and poorer-memory complaints. Earlier studies on image memory during aging were performed under non-naturalistic encoding conditions and thus may not reflect everyday memory performance. We have recently found that during naturalistic encoding younger adults' visual memory is much poorer than typically assumed and is influenced by physical image properties as size. Here we examined how visual memory during naturalistic encoding is affected by age. 296 adults (aged 18-92) with extensive online experience freely viewed images of different sizes while not being aware that

their memory will be tested later. Additional 72 adults (aged 18-91) with extensive online experience underwent a more typical visual memory study. Across all age groups image memory was affected by image size and was much poorer than found earlier. Surprisingly, no adverse effect of age on memory was found in any of the studies. While these results were obtained with highly experienced online participants, they highlight the importance of physical image properties on image memory across all age groups and indicate that image memory can be preserved during aging.

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DURING MORE NATURALISTIC ENCODING VISUAL MEMORY IS SUSCEPTIBLE TO MULTIPLE INFLUENCES

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Although studies show that human visual memory for object images is phenomenal during active engaging encoding, it is still unclear if this reflects memory during naturalistic visual behavior. We have consistently found that during naturalistic encoding, image memory is much poorer than the levels reported earlier and that the knowledge that an image was not seen before was much higher than memory for already-seen images. Here in a set of comprehensive experiments (n=249) we parametrically examined whether during more naturalistic-like encoding, memory for object images is robust or susceptible to multiple factors. We replicated our earlier findings with object images (lower overall memory and higher precision for image novelty than for remembering an image). During these less engaging encoding conditions memory was significantly affected by the number of images people were previously exposed to and by the number of novel images the previously-seen image was tested amongst. While our capacity for remembering new images can reach outstanding levels during highly engaging and controlled conditions, our results indicate that during more naturalistic-like less-engaging conditions, image memory is much weaker and susceptible to multiple influences. We assume that much less of the novel information we come across everyday actually registers in memory.

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Image memory capacity during naturalistic encoding is much lower than previously assumed

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Humans have outstanding image memory capacity for remembering even thousands of images. However, these findings are based on highly demanding experiments and may not reflect memory during daily vision. We have recently examined image memory during conditions that try to mimic daily visual encoding (freely viewing images while unaware that memory will be tested later, aka naturalistic encoding) and found that the overall memory levels were very low even when viewing only 160 images (≤60%, n=361). Here we aimed to estimate the number of images a person remembers during daily vision. In four experiments participants (n=143) naturally encoded 4 or 160 images from different categories and were later given a surprise recognition memory test. In line with our previous findings we consistently found that visual category affected memory (faces best remembered, outdoor images the least). Expectedly, memory for the 160 images was low (<60% for each of the categories, n=60). However, unexpectedly, memory for the 4 images did not reach ceiling performance (85%-90% remembered, n=83). As during naturalistic behavior people are likely less engaged in the images they come across than while participating in experiments, we assume only a small fraction of the images people view everyday is effectively remembered.

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Image size and exposure time affect memory but not perception performance

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Human image memory is considered having outstanding storage capacity with low sensitivity to physical image properties (e.g. size). However, these memory attributes are based on studies employing instructed-encoding tasks. In contrast, we have recently found that during naturalistic encoding, free of task-based modulations, image memory was affected by physical image properties as size and was much lower than previously found. Since visual memory relies on perception, one possibility is that memory performance during naturalistic encoding simply reflects poor perceptual processes. Therefore, here we examined whether perceptual measures are modulated by image size and whether memory performance is predicted by them. During encoding participants (n=45) were asked to report for each image (sized 3-15.5 deg.) whether there was a person in it and whether it was indoors or outdoors. Afterwards, participants were given a surprise recognition-memory test. Perceptual performance was at ceiling independently of image size, but memory significantly increased with image size. Comparable results (perception at ceiling but memory significantly affected) were obtained with exposure time modulations (250-2000ms, n=38). Although the less physically salient images allowed reaching ceiling perceptual performance, our results suggest that higher physically-salient images likely lead to higher quality signals across processing stages, resulting in higher memory.

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Lost in translation: ego-allo reference frame transformation is distinct from allo-ego translation

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The ability to create and maintain accurate spatial representations is crucial for navigation and orientation, yet individual differences in these skills are significant. Understanding the factors that contribute to this variability is essential. A key distinction in navigation research is between egocentric (self-centered) and allocentric (world-centered) reference frames, which are believed to engage different neural circuits. This study investigates the relationship between these reference frames and their contributions to spatial orientation by examining the translation process between them, while considering the often-overlooked variable of memory load. We conducted a virtual reality (VR) experiment consisting of two parts: first, participants explored dark virtual arenas using auditory cues to locate objects, then drew a map translating egocentric to allocentric information. In the second part, participants were provided with a map of object locations and indicated where those objects would be from their perspective, translating allocentric to egocentric information, with variations in memory load. Our results demonstrate that these transformations are behaviorally distinct and that memory load interacts with them in complex ways that differ among individuals. These findings enhance our understanding of spatial ability mechanisms and may inform research on spatial deficits in conditions like Alzheimer's disease.

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Contractive and repulsive perceptual biases as a function of reaction time

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Objectives: Perception is largely and systematically influenced by stimulus history, in particular by the most recent stimulus (recency bias). However, conditions under which the current percept is attracted to or repulsed from the previous stimulus remain unclear. This study investigates the impact of performers' strategies on the recency bias direction.

Methods: We administered a 2-face serial discrimination task using a uniform distribution of face stimuli created by morphing between two female identities ("Dafna" and "Liat"). Participants were asked to determine which face was more similar to Liat. In one counterbalanced half of the experiment, participants were instructed to prioritize accuracy over speed, and, in the other half, to prioritize speed over accuracy.

Results: We found a significant correlation between bias by recent faces and reaction time ($r=0.54$, $p<0.0001$). Quicker (slower) performance led to a more repulsive (contractive) recency bias, respectively. Quicker performance also resulted in a more contractive bias towards the closest prototype (Dafna or Liat).

Conclusions: Our results demonstrate a relationship between bias sign and magnitude and the available resources (RT). Limited resources (shorter RT) lead to initial prototype learning and repulsion from previous trial, enhancing prototypes. Increased resources (longer RT) lead to gradual learning of more morphed faces, enriching prior belief distribution.

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Molecular Mechanisms of Drive Accumulation: Role of Orb2 Protein in Behavior Regulation

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Motivation is a neuronal representation of internal state that directs goal-directed behaviors, ensuring they are appropriately timed, scaled, and contextualized. It is crucial to animals in many aspects of life like survival and food acquisition. While much is known about the neurobiology of motivation, mechanisms through which drives accumulate over time to control graded responses remains unclear. Nobel laureate Konrad Lorenz introduced a conceptual framework for drive accumulation called the hydraulic model. This model draws an analogy between motivation to fluid dynamics, suggesting that motivational energy accumulates like fluid and is eventually released through specific behaviors. But whether biochemical mechanisms supporting this model exist is yet to be tested. In this study, we explore the hydraulic model at the molecular level within a specific group of neurons known to encode various drives, the NPF system in flies. We hypothesize that drive accumulation may be encoded at the neuronal level through the oligomerization of a potential drive factor, the prion-like protein Orb2. This protein undergoes state-dependent aggregation, which could regulate local protein synthesis in active synapses. Our preliminary results indicate that a point mutation in Orb2, specifically phenylalanine to tyrosine (Orb2AF5Y), which reduces amyloid-like oligomerization, alters feeding patterns both at the basal level and in response to starvation. The effects of this mutation vary depending on its expression location, such all cells versus NPF neurons. Additionally, the JJJ2 chaperone protein facilitates Orb2 oligomerization. Expression of JJJ2 in NPF neurons led to decreased feeding in response to starvation while having no effect on basal feeding levels. Overall, our findings provide new insights into the molecular mechanisms underlying drive accumulation and offer potential avenues for further research into the regulation of motivational states.

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COLOR INCREASES IMAGE MEMORY DURING NATURALISTIC ENCODING

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The factors that contribute to image memory are far from being understood. Earlier studies found that factors such as image category semantic information influence memory but physical stimulus saliency has not been considered to substantially contribute to memory. We have recently found that during naturalistic encoding the physical dimensions of image size, contrast and presentation time significantly affect memory. Since color is another measurable/manipulable physical image property/dimension that affects image processing, here we assumed that it would contribute to image memory such that color images will be remembered more than colorless (grayscale) images. We also assumed that food images that are supported by a network in high-level visual cortex that is anatomically overlapping a network sensitive to color, color influence on memory will be modulated by visual category with the highest influence on food images. We found (n=78) that during naturalistic encoding color significantly influenced image memory and memorability and its influence was significantly modulated by category with food images being affected the most. Our results further substantiate the idea that physical saliency plays an important role in memory and indicates that enhancing stimulus saliency across multiple physical dimensions increases the probability of registration to memory during naturalistic visual behavior.

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Insight learning in a maze

Prof. Tom, Schonberg, Tel Aviv university

Prof Pablo Blinder, Tel Aviv university

Mr. Yehuda Bergstein, *Tel Aviv university*

The phenomenon of "sudden insight" or "Aha!" moments has been widely studied, especially in verbal and semantic contexts, such as remote association tasks. However, insights into spatial abilities, such as spatial navigation, remains less explored. In the current study we investigated whether a novel maze paradigm in virtual reality (VR) could elicit and objectively measure "insight" during spatial problem-solving. We collected a sample of n=32 participants that performed a maze we developed in VR. They completed the maze 10 times inside a unique Arena in the TAU XR center. Results show that most participants reported experiencing an "insight" moment, often pinpointing to the specific trial during which it occurred (Average trial 4.5/10). Notably, performance measured as the number of nodes (decision points) passed to the target improved objectively ($p<0.032$) in the trial following the average reported "insight" event, highlighting the tangible impact of insight on spatial problem-solving. This also highlights the ability to combine objective navigation measures with self-report in humans. We aim to replicate our findings and deepen our understanding of insight within spatial contexts through cross-species comparisons with mice, using objective "insight" measures and combining them with the unique human introspection. This approach could inform the process of sudden insight across multiple human learning tasks.

Topic 9

Learning and memory: Cellular mechanisms

DYNAMICS OF SERIAL DEPENDENCE DURING LEARNING

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Recent perceptual experience biases current perceptual decisions. This effect, termed 'serial dependence', has been observed in humans and animals, and across multiple sensory modalities. Distinct effects of serial dependence have been attributed to specific perceptual features (e.g., the previous stimulus or previous choice). However, it is unclear how serial dependence develops during learning. Here, we tested serial dependence of heading perception in four monkeys using either visual or vestibular self-motion stimuli. First, the monkeys were trained to discriminate whether the stimulus headings were leftward/rightward of straight ahead. In this 'regular' heading discrimination paradigm, the headings were independently distributed across trials. Then they were tested using an 'adaptive' paradigm, in which batches of sequential trials were biased either to the left or right, to expose a compound effect of several trials. During the learning process (in the regular paradigm), the effects of previous stimulus and previous choice evolved opposite directions. Specifically, in the early stages of learning, the 'previous choice' had a repulsive effect on the current choice; but, this was absent after training. By contrast, the previous stimulus initially had no

effect on the current choice; but, late in the learning process a repulsive effect emerged. These dynamics were seen in both the visual and vestibular modalities. In the adaptive paradigm previous (biased) stimuli elicited a repulsive effect and the corresponding previous choices elicited an attractive effect on the current choice, in both modalities. This pattern of results was compatible with observations in humans performing the same paradigm. In summary, the effects of serial dependence are dynamic and develop over learning. The transition of bias-dominance from previous choice to previous stimulus accompanies monkeys' enhanced performance, and might reflect increased certainty regarding the task rules. Moreover, at the steady state, the distinct (opposite) effects of previous stimuli and previous choices generalize across monkeys and humans, and visual and vestibular modalities.

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Ketosis as a potential treatment for traumatic brain injury in mice

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Traumatic brain injury (TBI) is a brain dysfunction without present treatment. Ketosis is a metabolic state characterized by elevated levels of ketone bodies. It is a response to low glucose availability, such as fasting, ketogenic diet (KD), or ketone ester supplements (KE). The goal of this study was to examine whether ketosis by KD or KE is neuroprotective in the TBI mouse model. We utilized a closed head injury model to induce TBI in mice, followed by up to 30 days of KD/KE. Elevated levels of ketone bodies were confirmed in the blood following KD and KE. Cognitive and behavioral performance, Y maze and Novel Object Recognition, were assessed post injury, and molecular and cellular changes were assessed within the temporal cortex and hippocampus. TBI mice maintained on KD displayed better cognitive abilities and elevated SIRT1 levels compared to a standard diet. In addition, KD management attenuated TBI-induced astrocyte reactivity in the dentate gyrus and decreased degeneration of neurons in the dentate gyrus and in the cortex. Our results support accumulating evidence that KD may be an effective approach to increasing the brain's resistance to damage, demanding further research into the origin of ketosis whether KD or KE.

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Memory recovery effect of innovative combination in Alzheimer's dementia

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Objectives: Alzheimer's disease manifests itself as a complex pathological condition with neuro-inflammation, oxidative stress and cholinergic dysfunction being a few of the many pathological changes. Due to the complexity of the disease, current therapeutic strategies aim at a multi-targeted approach often relying on combination of substances with versatile and complementary effects.
Methods: In the present study, patented by us innovative combination consisting of immune supporting complex, α-lipoic acid, citicoline, vitamin D3, selenium, extracts of leaves from olive tree and green tea, was investigated in scopolamine-induced Alzheimer's type dementia in rats, using behavioral and biochemical methods.
Results: We demonstrated that as compared to its components, the experimental combination was the most efficient in improving short- and long- term memory as assessed by the step-through test as well as spatial memory assessed by T-maze and Barnes maze, underlied by statistically significant decreases in acetylcholinesterase activity and lipid peroxidation; increases in superoxide dismutase activity in cortex;

increases in catalase and glutationperoxidase activities and BDNF and pCREB levels in hippocampus.

Conclusion: No significant histopathological changes, erythrocytes or blood parameter changes were detected, making the experimental combination effective and safe candidate in a multi-targeted treatment of Alzheimer's type dementia.

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HE ROLE OF INTERSECTIN-1 IN PREFRONTAL CORTEX SYNAPSES IN THE BASOLATERAL AMYGDALA IN FEAR MEMORY EXTINCTION

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prof. Raphael Lamprecht, Laboratory head (Laboratory for Molecular Neurobiology of Memory)- University of Haifa

Intersectin-1 (ITSN1) links endocytic membrane trafficking to actin assembly and acts as a guanine nucleotide exchange factor (GEF) for Cdc42, influencing synaptic transmission and morphogenesis. To explore the role of Intersectin-1 in memory formation, we conducted multiple experiments using a photoactivatable Intersectin-1 DH domain (PA-Intersectin-1). Intersectin-l functions through its DH domain as a GEF for Cdc42. We designed an optogenetic system to activate PA-Intersectin-1 in specific cells in vivo. We expressed PA-Intersectin-1 under the control of a CaMKII promoter using an AAV vector. PA-Intersectin-1 was expressed in the basolateral amygdala (BLA) and activated in excitatory neurons during fear conditioning to study its effect on long-term fear memory formation. Additionally, we expressed PA-Intersectin-1 in prefrontal cortex (PFC) synapses located in the BLA and examined its roles in memory extinction. Our findings show that PA-Intersectin-1 activation in the BLA excitatory neurons does not affect fear memory formation. However, activation of PA-Intersectin-1 at PFC-BLA synapses impairs fear memory extinction. This study shows the role of Intersectin-1 in PFC-BLA synapses in long-term fear memory extinction, providing insights into memory extinction mechanisms and potentially paving the way for developing therapeutic approaches for memory-related disorders.

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The cellular mechanism underlying dominant aversive memory

Ashutosh Ahire, Deborah Daphne, Iris Reuveni, Prof. Edi Barkai

Haifa University

Background: We recently reported experimental and theoretical evidence for a long-term mechanism that amplifies the response of a subset of neurons that were recruited during the learning of a complex task. We have termed this mechanism as "memory amplification mechanism". This mechanism is mediated by doubling of the strength of all inhibitory and all excitatory synapses in the cell. The key function of the amplification mechanism is to promote an already formed memory to a dominant memory. Aim: Our aim was to study if the amplification mechanism is selectively induced on those subsets of neurons that compose the fear-memory.

Methods: We recorded miniature synaptic events using whole-cell patch clamp recordings from neurons in the lateral amygdala of a transgenic mouse model that labels neurons that express the immediate early gene arc (arc dVenus) following the retrieval of the fear-memory.

Results: We found that the amplitudes of both excitatory and inhibitory synaptic currents were doubled selectively in the neurons that were tagged with the arc-dvenus after the retrieval of the fear- memory. The increase synaptic strength was mediated by a CaMKII dependent twofold increase of the conductance of all AMPA and GABA A receptors in the cell.

Conclusion: The dominant aversive memory is maintained by a sub-group of neurons on which all synaptic inputs, inhibitory and excitatory are doubled. Taken together with our previous findings, such across the board strengthening is controlled by a whole-cell rather by a synaptic specific process and is mediated by post synaptic CaMKII mediated enhanced channel conductance.

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THE MOLLUSCANS' 5-HT DEPENDENT SYNAPTIC PLASTICITY IS CONSERVED IN THE OCTOPUS' LTP MECHANISM

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The octopus' vertical lobe (VL) is responsible for learning and memory. Similar to the mammalian hippocampus, it exhibits an activity-dependent LTP that occurs at the synapses between the inputs pathway and simple amacrine interneurons (SAMs). A unique molecular switch mechanism mediates NO-dependent LTP expression and maintenance through a persistent NO-synthase (NOS) activation (Turchetti-Maia et al., 2018). Yet, the mechanism of LTP induction i.e., how activity turns on the switch, remains unclear. Following the discovery that the SAMs innervate serotonergic processes (Bidel et al., 2023), we hypothesized that activated SAMs, evoke 5-HT release which, via extrasynaptic transmission, switch on NOS only in the activated SAMs. The possible involvement of 5-HT in LTP induction was tested using two 5-HT receptor antagonists; methiothepin and spiperone which in Aplysia inhibit the cAMP-PKA and PKC pathways, respectively. Spiperone attenuated LTP induction, while methiothepin had no effect suggesting the involvement of 5-HT-dependent PKC-activation in LTP induction. To test if the cholinergic SAMs evoke the release of 5-HT, we applied ACh receptor antagonist (hexamethonium) which, indeed, attenuated LTP induction, which could be partially rescued by exogenous 5-HT. These results suggest that the cognitive abilities of the octopus have evolved through adaptation of conserved molluscan mechanisms.

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Sex Differences via Gene Expression Analysis in the Mouse Medial Amygdala

Isaac Berez, *Technion*

The medial amygdala is known to exhibit sexual dimorphism in size and morphology but less is known about differences at the cellular and genetic level. Here we sample the mouse medial amygdala from male, female, parent and virgin mice and employ single cell RNA sequencing (sc-RNA-seq) to discover a highly diverse cellular landscape across major neuronal and non-neuronal cell types. We validate our results with several other scRNA-seq amygdala based datasets via correlation analysis. To analyze gene expression differences between groups, we employ the mann-whitney U test and reveal at least 9 statistically significant, sexually dimorphic genes in GABAergic class. Collectively, these findings may offer insights behind many sex-biased psychological and neurological disorders, e.g. Alzheimer's and PTSD.

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All-optical electrophysiology reveals behavior-dependent dynamics of excitation and inhibition in CA1

Qixin Yang, *Edmond and Lily Safra Center for Brain Science*
Shulamit Baror-Sebban, Edmond and Lily Safra Center for Brain Science Rotem, Kipper, Edmond and Lily Safra Center for Brain Science Mickey, London, Edmond and Lily Safra Center for Brain Science Yoav, Adam, Edmond and Lily Safra Center for Brain Science

Neuronal integration in the hippocampus is dynamically modulated by behavior, shaping spiking output and gain through changes in excitatory (E) and inhibitory (I) inputs. Using simultaneous voltage imaging and optogenetic depolarization in genetically defined cell types, we characterized the input-output functions of key excitatory and inhibitory neurons within CA1 of awake-behaving mice. Locomotion decreased firing rates in pyramidal cells (PCs) and vasoactive intestinal peptide (VIP)-expressing interneurons, while increasing activity in somatostatin (SST) and parvalbumin (PV)-expressing interneurons. Subthreshold theta oscillations were predominantly driven by excitation in PV and SST cells, and by inhibition in PCs and VIP cells. Behavioral state modulated neuronal gain, as revealed by firing rate-intensity (F-I) curves, with PCs exhibiting significant gain modulation during locomotion. Notably, this modulation was specific to bursting activity, leaving simple spikes unaffected. A two-compartment model suggested that this burst-specific gain modulation arises from a balanced increase in E/I inputs to somatic and dendritic compartments. Lastly, we developed a classifier to identify cell types with high accuracy based on depolarized spike waveforms. These findings provide a detailed view of how CA1 neurons dynamically regulate activity, E/I balance, and theta oscillations, while showcasing the potential of voltage imaging in dissecting hippocampal circuit function.

Topic 10

Learning and memory : Network mechanism

Homeostatic regulation and dysregulation of CA1 neuronal activity and its role in contextual fear me

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Homeostatic regulation of neural circuits is believed to be crucial for maintaining optimal activity levels in response to a wide range of perturbations. However, how activity homeostasis of excitatory neurons is regulated in response to a chronic deficit in inhibition in the hippocampus of behaving mice remains unknown. To study those questions, we employed Ca2+ microendoscopy, electrophysiology, and chemogenetic chronic manipulation of CA1 interneurons in freely behaving mice. We found that CA1 excitatory population activity is not renormalized during 5 days of chronic inhibition of hippocampal interneurons. This is in contrast to chronic chemogenetic activation of interneurons resulting in renormalization of CA1 activity on the 4th day of the perturbation. Notably, the effect varied depending on the vigilance state, with a more pronounced effect observed during active wakefulness in comparison to quiet wakefulness and NREM sleep. Surprisingly, the inhibition of interneurons did not affect fear memory in the acquired context but instead led to increased fear generalization to a neutral context, with incompatible activation of memory-related cells in the neutral context. These results point to the necessity of inhibition in activity homeostasis of CA1 excitatory neurons and in contextual memory precision.

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THE REPRESENTATION OF RECURRING INFLAMMATORY EVENTS IN THE BRAIN

Tom Haran , *Technion*
Asya Rolls , Technion

Objectives: Our group has recently demonstrated that neuronal ensembles in the brain carry immune-related information (immunengram), which can drive specific peripheral immune responses. However, the development of the immunengram over time, especially in the context of recurring inflammations, has not been investigated to date. This is highly relevant for inflammatory diseases, which often exhibit chronic or relapse-remission dynamics. Our aim is to explore how repeated inflammatory reactions are represented by the brain.

Methods: We subjected mice to different inflammatory histories (single vs repeated exposures) and induced the expression of reporter genes in active neurons at the peak of the last inflammation via the TRAP system. We then cleared the brains and imaged them using light sheet microscopy to render a 3D representation of the immune representation at the whole brain.

Results: Several brain regions showed lowered numbers of active neurons in mice that underwent several inflammatory events. The TRAPed neurons in these mice were more likely to express cFos during a subsequent immune challenge.

Conclusions: Repeated inflammatory events induce changes in the immunengram, such that it becomes sparser and more readily activated. This may indicate that the representation of immune-related information in the brain is dynamic and changes throughout life.

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Plasticity in Auditory Cortex During Fatherhood

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Parental care is a fundamental and highly prevalent behavior observed throughout the animal kingdom, spanning from lower vertebrates to humans. This behavior is often sexually dimorphic and varies significantly across species and strains. In mammals, females typically serve as the primary caregivers; however, 3-5% of mammalian species also exhibit paternal care. Males undergo a significant behavioral transition upon becoming fathers, shifting from infanticide of pups to engaging in paternal care. To investigate the mechanisms underlying this behavioral transition, we explored functional plasticity in the auditory cortex of male mice as they transitioned into fatherhood. Using longitudinal two-photon calcium imaging, we measured single-neuron responses to pup calls and their corresponding narrowband noise (NBN) before, during, and after fatherhood. We observed a significant, albeit transient, improvement in neuronal discriminability between pup calls and NBN in fathers. To uncover the hormonal mechanisms driving these neuronal changes, we conducted a series of molecular, transcriptomic, and metabolomic analyses in the auditory cortex. Our findings revealed that several hormones exhibit differential levels during fatherhood compared to pre- or post-fatherhood stages. Notably, the receptor for the hormone prolactin demonstrated a significant and transient increase in activation specifically in the auditory cortex during fatherhood. To test whether prolactin contributes to the observed improvement in neuronal discriminability in fathers, we manipulated prolactin levels in vivo while recording auditory cortex responses to pup calls. We found that the speed of discrimination was compromised following the inhibition of prolactin secretion, and this effect was reversed upon prolactin administration. Advisor: Prof. Adi Mizrahi

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EFFICIENT PERFORMANCE AND INTERPRETABLE SPACE REPRESENTATION BY NEURAL NETWORKS TRAINED TO FORAGE

Noam Dotan, *Weizmann Institute of Science*
Elad Schneidman, Weizmann Institute of Science

The ability to forage, a fundamental “biological task”, implies some internal representation of the environment. Understanding how foraging may be carried out is beneficial for delineating how organisms represent space and the computations that underlie their ability to navigate, maximizing objectives given search costs such as energy or time. Here, we train artificial neural networks to forage, and then analyze their behavior and learned representations. Using supervised learning, we show that networks that rely on Long Short-Term Memory (LSTM) architectures can be trained to imitate infotaxis, a robust and efficient algorithm for tracking a stationary particle-emitting source in a turbulent environment, obtaining 94% accuracy in choosing the same action along search trajectories. Interestingly, we show that in some cases, networks trained to imitate infotaxis learned an interpretable representation of their search space, including spatially tuned neurons. We further employ deep reinforcement learning to train neural networks to find a weak source in such turbulent environments. We investigate how the source and the environment characteristics, as well as the chosen utility function, affect the networks’ learned behavior and space representations, and evaluate the networks’ performance in terms of the mean search time and the success rate of finding the source.

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Representational drift In biologically plausible learning rules

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We previously showed that representational drift could be partially a result of implicit regularization imposed by noise. This means that a complex learning system which has a degenerate solution space will travel along this space in a directed manner when exposed to noise. We now set out to expand our notion of learning such that it will be applicable to biological systems. These do not necessarily minimize a cost function, but rather implement a set of rules that modulate the system. We consider an arbitrary non-linear dynamical system with a conitnuous set of stable fixed points, which can be thought of as a null-space, and introduce noise to the dynamics. We charchtarize the movement along the continuous minima, and search for any type of directed movement. We find that a major difference between gradient based learning rules and biologically plausible rules is the orthogonality the Jacobian's eigenvectors along the null-space. Perliminary results show that, for a high enough dimension, fast orthogonal eigenvectors can impose a bias in the random walk along the null space.

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OPTOGENETIC STIMULATION OF CA1 DOPAMINE INPUTS DISRUPTS THE SPATIAL CODE IN A FAMILIAR ENVIRONMENT

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Dopamine plays a crucial role in learning. In the hippocampal CA1 region, dopamine is released from axonal projections arising from the ventral tegmental area (VTA) and from the locus coeruleus (LC). Hippocampal dopamine is known to enhance the short-term stability of spatial representations. However, the temporal dynamics of dopamine release in the hippocampus remain unknown. It is also unknown whether dopamine plays a role in the long-term stability of CA1 spatial representation over weeks. To address this, we combined Ca2+ imaging with optogenetics to monitor a large cell population in hippocampus CA1 while stimulating dopaminergic projections in freely moving mice as they traversed a familiar linear track. While stimulation of VTA dopamine projections during exploration of the linear track did not alter the rate of Ca2+ events, their amplitude, or the active cell count, it led to reduced stability of the spatial tuning compared to non-stimulated sessions. Our findings raise the possibility that dopamine, commonly linked to novelty or surprise, could play a role in memory encoding by creating a period of plasticity during which spatial representations become more distinct in comparison to previous less-salient events.

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Synaptic motility and functional stability in the whisker cortex

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The distribution of preferred phases of whisking neurons in the somatosensory system of rats and mice presents a conundrum: simple pooling models predict distributions that are an order of magnitude narrower than empirically observed. Thus, it remains unclear which mechanism generates this unexplained distribution. We studied the hypothesis that this distribution results from spike timing dependent plasticity (STDP), and explored STDP dynamics in the framework of a modeling study. Our investigation reveals that under a wide range of parameters, STDP dynamics do not converge to a fixed-point. Rather, synaptic weights continue to evolve in time. As a result, the preferred phases of the downstream population drift in time at a non-uniform velocity, which in turn induces a non-uniform distribution of preferred phases. In this manner, the distribution results from the continuous remodeling of synaptic efficacies. Furthermore, the relation between the STDP rule and the resultant distribution predicted by our theory provides a natural test of our hypothesis. Our theory suggests that the widespread synaptic motility observed in the brain, which has long been viewed as a hindrance that the brain needs to overcome, may actually be an underlying principle of the organization of the central nervous system.

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Memory consolidation by reactivation of human concept neurons during sleep reflects contents, not sequence of events

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How do our brains manage to store our everyday experiences into memory? Neurons in the human temporal lobe that respond to the concept of an individual person or object have been proposed to provide semantic building blocks for episodic memory. Recording from 1437 neurons in neurosurgical patients who learned a story involving specific concepts, we found reactivation of neurons representing these concepts during slow-wave sleep after learning. Concept neurons were conjointly reactivated, particularly during sharp-wave ripples, with time lags suitable for synaptic modification. However, the temporal sequence of reactivation did not reflect the sequence of concepts in the learned story. Unlike rodent place cells, which acquire preferred firing locations during exploration of new environments according to their pre-existing preferred sequence of activation, human concept neurons are tuned to specific semantic contents before learning starts. Consequently, pre-existing firing sequences correlate with consecutive place fields in rodents, but not with sequences of events in human experience.

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Voltage imaging of excitatory and inhibitory Hippocampal neurons during global remapping

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Hippocampal place cells are thought to comprise the building blocks for a cognitive map of space. Conducting parallel intracellular recordings from the diversity of hippocampal cell types can help elucidate the mechanisms underlying place cell formation. However, such recordings are essentially impossible using conventional electrode-based techniques. To address this challenge, we expressed the genetically encoded voltage indicator Archon1 in CA1 pyramidal cells (PCs) and dendrite-inhibiting Somatostatin (SST)-positive interneurons (INs) an recorded their membrane potential during navigation in familiar and novel virtual spaces. A large fraction of PCs exhibited spatial tuning in their firing, while SST INs displayed diverse activity profiles, with many of them tuned to the animals running speed, others showing uniform firing rates along the track, and a small fraction of spatially tuned cells. Transition to a novel space induced global remapping of the spatially tuned cells from both populations. To our surprise, the SSTs increased their global firing rates in the novel environment, suggesting that dendritic inhibition is increased during hippocampal remapping. These findings expand our knowledge of the activity and function of critical components of the CA1 microcircuit during spatial navigation and comprise a first step towards a detailed mechanistic understanding of hippocampal place cell formation.

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Higher-level (but not early) visual processing is associated with memory during naturalistic encoding

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We have found that during naturalistic encoding (without task-based modulations and with no awareness of the memory-aspect of the study) more physically-salient images (such as bigger or with higher contrast) are better remembered. We hypothesized that this follows the extent of visual system resources devoted to processing more physically salient images (e.g. bigger images activating bigger parts of visual system) and that this leads to higher signal to noise ratio feeding downstream to higher-level visual cortex and eventually to higher-level non-visual memory-related areas. However, it is unclear whether this memory performance is associated with activation in earlier or in higher visual processing stages. Modulating levels of image scrambling can dissociate earlier- and higher-order (ventral stream) visual areas' activations since increased scrambling is associated with stronger activation in earlier visual areas but with weaker activation in higher visual areas. Therefore, we used image scrambling to examine whether memory patterns follow earlier or higher-order visual areas activation patterns. In naturalistic encoding experiments (n=80) we measured memory levels for intact images (baseline) and for images with increased scrambling levels (up to 100x100 parts). Increased scrambling levels led to decreased memory. Our results highlight the importance of higher-level ventral visual areas in memory formation.

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CALCIUM IMAGING OF THE OCTOPUS VULGARIS VERTICAL LOBE

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The Octopus vulgaris Vertical Lobe (VL) and Superior Frontal Lobe (SFL) are crucial for visual learning and memory. The 1.8m axons from SFL make en passant glutamatergic synaptic connections with only ~12 of the 22m simple amacrine interneurons (AM) in the VL. Similarly to the hippocampus, the SFL-VL network possesses activity-dependent long-term potentiation (LTP), that is NMDA-independent and expressed by increased SFL glutamate release. 'Fan-out fan-in' feedforward organization and the prerequisite of LTP for memory was shown, but the network neural activity patterns during natural conditions/learning are unknown. We aimed to characterize the 'fan-out' SFL-AMs connectivity in calcium indicator-loaded slices by fluorescent microscopy and field potential recordings following the single-pulse (SP) or paired-pulse (PP) stimulation of SFL axons. PP stimulation shows sublinear Ca++ summation in the presynaptic axons followed by a supranonlinear postsynaptic response resembling the LTP induction and suggesting strong short/long-term facilitation of transmitter release. For the first time, we were able to monitor single AM-Ca++ signal and the number of cells lit up by a PP was dramatically increased compared to almost none after SP. This may imply that the temporal pattern of SFL axons spike trains encode significant features of sensory information.

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Novel off-context experience constrains hippocampal representational drift

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Alon Rubin, *Weizmann Institute*
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The hippocampus forms unique neural representations for distinct experiences, supporting the formation of different memories. In familiar environments, hippocampal representations gradually change over time as animals repeatedly visit the same environment (‘representational drift'). While the underlying mechanisms of representational drift are still not fully understood, a leading hypothesis suggests that it results from ongoing learning processes. Accordingly, because the brain uses the same neural substrates to support multiple distinct representations, learning of novel stimuli or environments leads to changes in the neuronal representation of a familiar one. If this is true, we would expect drift in a given environment to increase following new experiences in other environments (i.e., ‘off-context’). To test this hypothesis, we longitudinally recorded large populations of hippocampal neurons in mice while they repeatedly visited a familiar linear track over weeks. We introduced off-context experiences by placing mice in a novel environment for one hour after each visit to the familiar track. Contrary to our expectations, these novel episodes decreased place cells' representational drift. Our findings support a model in which distinct memories occupy different areas within the neuronal activity space, and their drift within it is constrained by the area occupied by other memories.

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'Timer-like' and 'calendar-like' time-coding schemes underlie within-episode dynamics in the hippocampus

Gal Elyasaf, Weizmann Institute Alon Rubin, *Weizmann Institute Yaniv Ziv, Weizmann Institute*

The hippocampus is critical for temporally linking events to form episodic memory, making its role in coding time a widely studied subject. However, different studies consider two fundamentally distinct concepts of time. Some consider "timer-like coding", where neurons represent the phase within a stereotypic and repetitive episode (e.g., "time cells" coding for timing within a fixed delay period). Others consider "calendar-like coding", where neural activity continuously changes without resetting relative to a local time frame (e.g., long-term "representational drift", which may facilitate the formation of a mental timeline of events in memory). Since both dynamics involve gradual changes, analyzing neuronal activity within a session cannot distinguish between these coding schemes. However, tracking the same neurons across days allows for this dissociation. We longitudinally recorded hippocampal neurons in mice that repeatedly explored a familiar environment over weeks. Quantifying the contribution of the timer-like and calendar-like dynamics to the within-session drift revealed that both contribute significantly, but the timer-like component is more prominent. In addition, our findings suggest that a substantial portion of drift in spatial tuning across sessions occurs 'off-context', especially during sleep. Overall, our results quantitatively account for the contribution of distinct putative mechanisms for coding time in episodic memory.

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Chronic month-long operation of a brain-computer interface in the hippocampus CA1

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Weizmann Institute of Science

Brain-computer interface (BCI) systems allow direct feedback in response to neuronal activity and are used both for clinical applications and as research tools. In a typical BCI system, a decoder is pre-trained on a set of known neuronal responses and is then used for continuous online decoding of neuronal activity. A major challenge in chronic applications of BCIs is the need to frequently retrain the neuronal decoder, often on a session-by-session basis, due to changes in the neuronal population being tracked and representational drift. We implemented a chronic BCI system using Ca2+ imaging in the hippocampus CA1 of freely behaving mice housed in a home-cage-like environment. In the experiment, the BCI controlled the administration of drinking water, which was triggered by a specific neuronal population activity pattern that is associated with the location of the water port. We demonstrate that during a month-long period, a mouse successfully obtained drinking water solely through the BCI system. These results provide proof of concept of a stable, continuous BCI application that could operate over extended periods with minimal retraining and re-calibration. Such a hippocampal BCI offers a new approach to studying long-term memory via a closed-loop manipulation of its underlying neuronal representations.

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ENCODING OF TASTE VALENCE AND INTEROCEPTION IN THE INSULA

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David Manor, MRI Unit RAMBAM Health Care Campus Haifa
Shaked Rosenblum, School of Psychological Sciences University of Haifa
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The Insular cortex (IC) is involved in taste perception, interoception, and plays a critical role in associating taste stimuli with their after-effects, known as taste valence encoding. The anterior IC receives taste inputs, whereas the posterior IC receives interoceptive information. Taste is influenced by learned experiences, which assists in the evaluation of safety and the metabolic impact of food. The exploration of the brain's role in storing taste along with interoceptive information and its impact on physiology is an underexplored field in neuroscience. In addressing this gap, we recently found that connectivity from anterior to posterior insula subserves conditioned immune response in mice. To extend the findings to humans and to elucidate the functional similarities and differences in IC between the humans and mice, we utilize fMRI in young healthy humans. Our preliminary results in humans confirm the involvement of insula during imagination of taste and during perception of disgust. We further aim to explore functional connectivity within IC and with other regions during encoding of interoception to understand the IC's involvement in the encoding of taste, and in storing and modulating interoceptive information.

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Neural activity and learning-dependent dynamics of Lateral Septum neural populations during social interactions

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Dr. Yair Shemesh, Department of Neurobiology, Weizmann Institute
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The Lateral Septum (LS) is an evolutionary conserved ventral forebrain structure known to be implicated in a plethora of social interactions including aggression, kin recognition, social novelty preference, social fear/avoidance and others. Its input-output structure suggests a role as a key regulator of contextual/social information, which originates from associative areas such as the hippocampus (archicortex) and prefrontal (neocortex) and reach various hypothalamic nuclei, thus regulating behavioral output. While the LS is a predominantly GABAergic structure, its distinct sub-populations express various receptors of neuromodulator transmitters and hormones but can also exhibit dual neurotransmitter phenotype (GABA-Acetylocholine). In vivo studies describing the activity of distinct LS sub-populations are extremely sparse. Here, by utilizing transgenic mice in combination with opto-physiological methods and quantitative behavioral analysis, we show that distinct neuronal populations of the LS are differentially activated across various social interactions. Specifically, we find that Oxt-R+ LS neurons are differentially activated during various phases of aggression. Additionally, LS cells with an active mDlx promoter exhibit learning-dependent activity dynamics, manifested during social novelty preference and social fear conditioning. Lastly, we show that Chat+ LS neurons display opposing learning-dependent activity dynamics compared to the mDlx population after social fear conditioning.

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Egocentric navigation network plasticity: training extends functional connectivity of V6 to frontal areas of congenitally blind people

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Ariel University

Retinotopically organized visual area 6 (V6) processes optic flow in animals and humans. We previously demonstrated that V6 is a sensory independent area involved in egocentric navigation. Indeed, V6 of congenitally blind (CB) people encodes auditory input for egocentric navigation similarly to the way V6 of sighted people encodes visual cues. In the current study, rest functional connectivity was used to investigate training induced brain connectivity changes in CB participants. CB participants were scanned during resting state sessions before and after a three-day training period learning to navigate in mazes using the EyeCane, a sensory substitution device (SSD). Before training, functionally defined area V6 is connected with areas of the dorsal network while it is anti-correlated with mediotemporal areas, suggesting a 'division' between egocentric and allocentric spatial reference frames. After training however, V6 extends its connectivity to areas of the dorsolateral prefrontal cortex (9-46d) and anterior cingulate (24pr). These newly established connections may underlie the long-term plasticity observed in area V6 for processing auditory navigation cues, potentially reflecting the adaptation following training with the EyeCane and facilitating the acquisition of maze navigation skills. Our findings demonstrate that training can alter connectivity and induce long term plasticity in the dorsal stream. Since frontal areas are strongly involved in higher-order cognitive processes and in active control of planned behavior, results suggest that training the dorsal stream could be explored as a potential strategy to mitigate cognitive decline, especially for Alzheimer research since degeneration affects mainly the navigation network until reaching frontal areas.

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Topic 11

Models and Theory : Cellular

Single Neurons Can Solve The n-dimensional XOR Problem

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Various characteristics of single neurons, including pronounced dendritic tree morphology, nonlinear membrane ion channels, and nonlinear synapses are thought to expand the computational capabilities of single neurons. Detailed biophysical models accurately describe the input/output (I/O) function of single neurons. However, there are no efficient learning algorithms to implement specific I/O functions using biophysical models, which take advantage of the nonlinear dendritic properties. Here, we developed a learning rule for both the synaptic weights and the axon-synapse wirings for detailed biophysical models, using deep neural network (DNN) models as surrogates. Specifically, we explored the space of learnable parameters of the single neuron, spanned by both functional plasticity and structural plasticity, by utilizing surrogate differentiable DNNs on otherwise nondifferentiable detailed biophysical models. Using our approach, we show that a single neuron can solve the XOR problem, famously known to be unsolvable by the perceptron model. Furthermore, we introduce the n-parity task as a natural n-dimensional generalization of the XOR problem and establish that a single neuron can solve the n-parity problem for various n>2. Overall, our novel learning rule enables systematic exploration of the single neuron computational capabilities across diverse tasks.

Topic 12

Models and Theory : Network

Blood pressure pulsations modulate olfactory bulb neuronalactivity via mechanosensitive ion channels

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The transmission of heartbeat through the cerebral vascular system is known to cause intracranial pressure pulsations. Here we describe for the first time that arterial pressure pulsations within the brain can directly modulate central neuronal activity. Several lines of evidence have established the expression of a mechanosensitive ion channel within the mitral cell (MC) membranes, most likely Piezo2, pointing to a pressure pulsation transduction pathway within the Olfactory Bulb (OB). We record local field potentials (LFP) from the rat's OB using a semi-intact rat perfused nose brain preparation (NBP), while monitoring the pressure pulsations induced by a peristaltic perfusion pump which falls within the physiological range of heartbeat induced pulsations. Such pressure pulsations elicit local field oscillations in the olfactory bulb that are sensitive to hypoxia (n=13) and block of mechanosensitive channels TRPC/Piezo blocker D-GsMTx4 (n=13 NBPs, local injection). We find that MC spiking activity is synchronized to this mechanosensation signal (n=20 NBPs). Indeed, in awake animals, a subset of olfactory bulb neurons entrain their firing within ~20 ms window of the heartbeats. We propose that this intrinsic interoceptive mechanism can modulate olfactory activity sensitivity during arousal and influence brain activity on a wider scale.

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Cognitive flexibility requires past re-evaluation: theory and neural networks analysis

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Animals and humans can rapidly adapt their behavior to environmental changes, yet we do not have a firm understanding of how the brain supports this cognitive flexibility. Previous studies modeled adaptation to a changing environment in neural networks using an explicit context-specific input. However, more realistically, changes in the environment are implicit, and do not manifest in such inputs. Instead, states and contexts must be inferred from observations over time, which results in source-uncertainty - when a given observation can be generated by multiple state-context pairs. Here, we derive a theoretical framework for how an agent can resolve source-uncertainty by re-evaluating past observations. We then test our theory by training recurrent neural networks with reinforcement-learning to perform an implicit-context-dependent decision-making task. We show that state-context pairs are represented in the networks' activity, and that the network's policy rapidly maximizes reward rates. Most significantly, our theory and simulations explain model-based (reward independent) updating of latent variables that effectively solve the source-uncertainty problem. Overall, we show that re-evaluation of past observations is a possible mechanism for cognitive flexibility.

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Meso-scale Network Connectivity: Insights from Intracranial EEG during Rest and Task States

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Objectives: Connectivity across the brain, usually as measured with fMRI, has been shown to reflect functional organization and different brain states. Here we investigate meso-scale network connectivity with intracranial-EEG and its modulation during rest versus task states within a graph theory framework.

Methods: We used intracranial-EEG data from 45 epilepsy patients [1], recorded during rest (3 minutes) and task (watching a 6.5-minute movie). Time-resolved functional network connectivity was computed by assessing non-directed interactions through coherence between recording channels during rest and task [2]. We then applied graph theory Connectomics metrics on the adjacency matrix to extract network properties [3].

Results: Network connectivity matrices consisted of electrodes covering the parietal, frontal and temporal lobes (On average 77 for each patient, range 48-128). Overall coherence in the network across time points was larger during task compared to rest. Furthermore, average node degree and node strength were larger during task than during rest.

Conclusions: Our preliminary findings suggest that the configuration of the meso-scale network is modulated during task state compared to rest, and these changes can potentially be captured by network Connectomics features. Further research should investigate the dynamic changes in network configuration and the emergence of transient task states.

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Learning with Incomplete Models: Recurrent Neural Network Dynamics in Agent-Environment Interaction

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Omri Barak, Network Biology Research Laboratories & The Ruth and Bruce Rappaport Faculty of Medicine

Learning in both biological and artificial systems is shaped by the interaction between agents and their environments. Given the complexity of the world, agents often operate under partial observability, requiring them to construct internal representations to achieve their goals. These representations are not innate but emerge gradually through experience, creating a dynamic interplay between action and learning. While most research focuses on fully trained networks, the process of representation formation during learning remains underexplored. Additionally, many studies emphasize supervised learning (SL) in offline settings, overlooking the challenges posed by reinforcement learning (RL), where agents must simultaneously learn and act. In this work, we address these gaps by training recurrent neural networks (RNNs) on a navigation task requiring temporal integration. We compare the learning dynamics of SL and RL within the same task. Our findings reveal that both learning rules, when trained long enough, eventually lead to the same limit-cycle representation. However, the trajectory to this solution differs: in SL, an intermediate line attractor representation is sufficient to reach high accuracy, whereas in RL, the line attractor cannot achieve high accuracy, and the agent must progress to a limit-cycle representation to perform well. We discuss the implications of these findings in the context of training biological animals in neuroscience tasks.

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DBS Frequency Modulation and Its Impact on Thalamo-Cortical Network Interactions During Anesthesia

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Conscious experiences are thought to arise from interactions between thalamic and cortical networks, particularly involving the central lateral nucleus (CL), which connects with cortical layers and receives brainstem reticular activating system inputs. Previous studies show that DBS in the CL affects consciousness bidirectionally: 50 Hz restores arousal in anesthetized macaques, while 10 Hz and 200 Hz reduce consciousness in awake animals. My study explores how DBS at 10, 50, and 200 Hz influences the thalamo-cortical network under anesthesia, assessing its therapeutic potential for disorders of consciousness. Using a murine thalamo-cortical slice model, DBS was applied to thalamo-cortical (TC) and cortico-cortical (CC) pathways, revealing frequency-dependent effects. Low-frequency DBS (10 Hz) caused mild, consistent depolarization, while medium-frequency DBS (50 Hz) induced more significant depolarization. High-frequency DBS (200 Hz) produced variable effects, including both depolarization and hyperpolarization. Cortico-cortical responses also varied with frequency: 10 Hz enhanced CC EPSPs (EPSP ratio = 2.06, $p = 0.003$), 50 Hz showed a mild depressive trend (EPSP ratio = 0.90, $p = 0.085$), and 200 Hz effects were inconsistent ($p = 0.286$). These findings suggest that DBS frequency can selectively modulate neural activity and cortical excitability, highlighting its potential for treating disorders of consciousness.

Topic 13

Models and Theory: System

Amit Regev Krugwasser (Gonda Brain Research Center, Bar-Ilan University), Reina

van der Goot (*Gonda Brain Research Center, Bar-Ilan University*),
Geffen Markusfeld (Gonda Brain Research Center, Bar-Ilan University),
Yair Zvilichovsky (Gonda Brain Research Center, Bar-Ilan University),
Roy Salomon, Haifa University Neural Correlates of the Embodied Sense of Agency: A Pre-registered EEG Study

The Sense of Agency (SoA) is the subjective experience of control over one's actions. Two levels have been suggested in the formation of SoA, early implicit sensorimotor and later explicit higher-level processes. However, neural evidence for this model has hitherto remained limited. This pre-registered EEG study investigated the electrophysiological characteristics of SoA using time-frequency analysis and Multivariate Pattern Analysis (MVPA). Participants engaged in a virtual reality paradigm where visual feedback of a finger movement was modulated to create (mis)matches between expected and actual sensory feedback. Participants rated their SoA over observed movements with either anatomical (different finger) or spatial (angular shift) manipulations. As predicted, results demonstrated that increased sensorimotor conflict correlated with decreased alpha-band attenuation. MVPA successfully decoded reported agency with 68% accuracy, starting 200ms post-movement onset. Cross-decoding revealed shared neural patterns across agency manipulations, emerging 500ms post-movement. Our findings suggest reduced alpha attenuation is a signature of SoA loss. In addition, MVPA results support the hypothesis of a two-level SoA formation: an early, domain-specific component and a late, domain-general component. Our pre-registered EEG investigation of embodied SoA sheds light on the neural correlates of the mechanisms underlying it, expanding the knowledge base of this field.

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When predict can also explain: few-shot prediction to select better neural latents

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Latent variable models serve as powerful tools to infer underlying dynamics from observed neural activity. Ideally, one would like the inferred dynamics to equal the true ones. However, due to the absence of ground truth data, prediction benchmarks are often employed as proxies. In this study, we reveal the limitations of the widely-used 'co-smoothing' prediction framework and propose a remedy. Utilizing a student-teacher setup with Hidden Markov Models, we demonstrate that the high co-smoothing model space can encompass models with arbitrary extraneous dynamics within their latent representations. To address this, we introduce a secondary metric -- a few-shot version of co-smoothing. This involves performing regression from the latent variables to held-out channels in the data using fewer trials. Our results indicate that among models with near-optimal co-smoothing, those with extraneous dynamics underperform in the few-shot co-smoothing compared to 'minimal' models devoid of such dynamics. We also provide analytical insights into the origin of this phenomenon. We further validate our findings on real neural data using two state-of-the-art methods: LFADS and STNDT. In the absence of ground truth, we suggest a novel measure to validate our approach. By cross-decoding the latent variables of all model pairs with high co-smoothing, we identify models with minimal extraneous dynamics. We find a correlation between few-shot co-smoothing performance and this new measure. In summary, we present a novel prediction metric designed to yield latent variables that more accurately reflect the ground truth, offering a significant improvement for latent dynamics inference.

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Topic 14

Motor systems: Cerebellum

INTERACTIONS BETWEEM THE CORTICO-BASAL GANGLIA AND THE CORTICO-SEREBELLAR LOOPS DURING MOVEMENTS

Asia Prag - Edmond & Lily Safra Center for Brain Sciences
Henn Kramer - *Edmond & Lily Safra Center for Brain Sciences*
Nirvik Sinha - Edmond & Lily Safra Center for Brain Sciences
Yaniv Pasternak - Edmond & Lily Safra Center for Brain Sciences
Yifat Prut - Edmond & Lily Safra Center for Brain Sciences

Subcortical control of motor cortical activity is crucial for selecting and coordinating motor outputs. The two subcortical structures, cerebellum and basal ganglia (BG), send signals relayed through the motor thalamus to reach motor cortical areas in the frontal lobe. Little is known about the unique motor-related information transmitted through each of these systems and their mutual interactions when planning and executing movements. We trained a monkey to reach to pre-cued targets. In 20% of the trials, the target jumped to a new location after the 'GO' signal. Chronic stimulating electrode was implanted in the cerebellar output pathway and simultaneous recordings were conducted from the motor cortex and BG using multichannel linear probes. During task performances, BG cells (striatum, GPe and GPi) were task-related and directionally tuned around the Go signal. We also found a short latency (~5ms) striatal multiunit response to cerebellar stimulation, consistent with a direct (trans-thalamic) cerebellar-to-BG connection, in parallel to the cortico-striatum pathway. The results suggest that striatal encoding of movement kinematics could be driven by motor cortical and cerebellar inputs. Moreover, unlike the previous view of the cerebellum and Basal Ganglia as parallel loops, these structures interact in multiple levels and contain overlapping movement-related signals.

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THE CEREBELLUM FACILITATES BETA-BAND DESYNCHRONIZATION IN THE MOTOR CORTEX DURING REACHING MOVEMENTS

Nirvik Sinha, *Edmond and Lily Safra Center for Brain Sciences, Hebrew University of Jerusalem and Department of Physical Therapy and Human Movement Sciences, Northwestern University*

Abdulraheem Nashef, Anschutz Medical Campus, University of Colorado Denver Julius PA Dewald, Department of Physical Therapy and Human Movement Sciences, Northwestern University Yifat Prut, Edmond and Lily Safra Center for Brain Sciences, Hebrew University of Jerusalem

The local field potential (LFP) in the sensorimotor cortex is dominated by low-frequency beta-band oscillations (13-30 Hz). During voluntary movements, power in these frequencies reduces, indicating an increase in cortical excitability (beta-band desynchronization, beta-MRD). Previous studies have identified cortico-subcortical networks (chiefly the cortico-basal ganglia loop) as potential sources of beta-MRD. In this study, we explored the role of cerebellar output to primary (M1) and premotor (PM) cortices on beta-MRD during movements with varying postural demands. Five monkeys were trained to perform a center-out reaching task using their upper limb in two distinct modalities: supported planar-reach vs. unsupported free-reach. The cerebellar outflow was reversibly blocked using high-frequency stimulation (HFS, 130Hz) through an electrode implanted in the superior cerebellar peduncle. We then performed time-frequency decomposition of M1 and PM LFP activity to compare changes in beta-MRD during control vs. HFS trials. Beta-MRD in M1 were significantly reduced under HFS in both tasks. Notably, HFS was particularly influential in movements to higher targets in the free-reaching task. In PM, HFS reduced beta-MRD only during free reaching towards higher targets. Our findings thus indicate that intact cerebellar signals enhance movement-related beta-MRDs. This effect is area-dependent, contingent on the task-specific requirements for postural drive.

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INTERACTIONS BETWEEM THE CORTICO-BASAL GANGLIA AND THE CORTICO-SEREBELLAR LOOPS DURING MOVEMENTS

Asia Prag - *Edmond & Lily Safra Center for Brain Sciences Henn Kramer - Edmond & Lily Safra Center for Brain Sciences*

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Yaniv Pasternak - Edmond & Lily Safra Center for Brain Sciences Yifat Prut - Edmond & Lily Safra Center for Brain Sciences

Subcortical control of motor cortical activity is crucial for selecting and coordinating motor outputs. The two subcortical structures, cerebellum and basal ganglia (BG), send signals relayed through the motor thalamus to reach motor cortical areas in the frontal lobe. Little is known about the unique motor-related information transmitted through each of these systems and their mutual interactions when planning and executing movements. We trained a monkey to reach to pre-cued targets. In 20% of the trials, the target jumped to a new location after the 'GO' signal. Chronic stimulating electrode was implanted in the cerebellar output pathway and simultaneous recordings were conducted from the motor cortex and BG using multichannel linear probes. During task performances, BG cells (striatum, GPe and GPi) were task-related and directionally tuned around the Go signal. We also found a short latency (~5ms) striatal multiunit response to cerebellar stimulation, consistent with a direct (trans-thalamic) cerebellar-to-BG connection, in parallel to the cortico-striatum pathway. The results suggest that striatal encoding of movement kinematics could be driven by motor cortical and cerebellar inputs. Moreover, unlike the previous view of the cerebellum and Basal Ganglia as parallel loops, these structures interact in multiple levels and contain overlapping movement-related signals.

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Topic 15

Motor systems : Motor cortex

THE ROLE OF M2 CORTICOSPINAL PYRAMIDAL TRACT NEURONS IN LEARNING AND MOTOR CONTROL

Sivan Geva, *Israel Institute of Technology, Technion*

The mouse primary motor cortex's layer 5 corticospinal pyramidal tract (PT) neurons are crucial for motor control and executing motor commands. Recent findings suggest additional connections from layer 5 PT neurons in the secondary motor cortex (M2) to the spinal cord. Our study aims to investigate M2 corticospinal PT neuron's role in motor control and learning, exploring whether they create parallel pathways with distinct functions alongside M1 neurons. We will record PT neuron activity from both M1 and M2 while mice learn a hand reach task, analyzing their representation and how different inputs affect their activity and motor performance. To achieve this, we will employ advanced techniques, including two-photon calcium imaging, viral neuronal tracing, and in vivo optogenetics. These cutting-edge methods allow precise examination of corticospinal PT neurons in both motor cortexes. This research offers insights into potential parallel circuitry of corticospinal PT neurons from M2, advancing our understanding of neural mechanisms in motor control. It may open avenues for therapeutic interventions targeting these neurons in the future.

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INTERPRETABLE NETWORK ANALYSIS OF THE MOTOR CORTEX DURING PERFORMANCE OF A MOTOR TASK

Shira Lifshitz, *Technion*
Ram Dyuthi Sristi, UC San Diego, Ofir Lindenbaum, Bar-Ilan University
Maria Lavzin, Technion, Jackie Schiller, Technion
Gal Mishne, UC San Diego, Hadas Benisty, Technion

In this study, we explore the representation of outcome in layers 2-3 of the primary motor cortex (M1) in mice performing a hand-reach task. Previous work indicates that M1 neurons encode trial-by-trial binary outcome with distinct populations reporting success or failure. In this work, we investigate the relationship between the encoding of binary outcome and the encoding of its value, represented by flavor. We analyzed data from 2-photon calcium imaging experiments of mice reaching to retrieve flavored food pellets: grain, quinine, sucrose, and fake (plastic). We applied a novel deep-learning model for contextual feature selection termed Conditional Stochastic Gates (c-STG) to identify specific neuronal populations that encode task-relevant information. Using a single model, rather than thousands of classical models as done before, we confirmed previous findings of binary outcome encoding. Then we show that introducing flavored food pellet induced a change in the way the network in Layer 2-3 reports outcome. At the first exposure, the network reports novelty vs. familiar where new flavors are grouped together regardless of value. During repeated exposures to flavored pellets network dynamics shifts towards reporting value where aversive flavors are grouped together as different from pleasant ones.

Topic 16

Motor systems: Posture and gait

DECIPHERING INTEGRATIVE PROPERTIES OF LAYER 5 PT NEURONS IN THE PRIMARY MOTOR CORTEX OF MICE

Pratibha Ahirwal, *Technion*
Yara Otor, Technion
Jackie Schiller, Technion

Primary motor cortex pyramidal neurons comprise diverse cell types, differing in location, projections, gene expression, and electrophysiology. Layer 5 thick-tufted pyramidal tract (PT) neurons directly control behaviour by transmitting motor cortex output to brainstem, thalamus, and spinal cord. Mouse motor cortex PT neurons divide into three sub-populations based on molecular markers and axonal projections: one projects to the medulla, another to the thalamus, and a third to both regions. Recent study from our lab (Otor et al., 2022), revealed two distinct populations of PT neurons with respect to motor representation and dendritic anatomical properties: type-1 with early bifurcation and long nexus, and type-2 with late bifurcation and short nexus. Type-1 neurons exhibit compartmentalized tuft function, while type-2 neurons demonstrate synchronous tuft activation. A substantial proportion of M1 cortico-spinal PT neurons projecting to the medulla exhibit type-1 dendritic morphology. Retrograde viral tracing and anatomical reconstruction showed that M1 cortico-spinal PT neurons exhibit a high proportion of type-1 dendritic morphology, with 90% of reconstructed neurons in 4 mice belonging to type-1 neurons. This study aims to classify the two types of PT neurons we described into the known classifications based on their projection targets and to discern their specific dendritic biophysical properties.

Topic 17

Motor systems : Subcortical: basal ganglia

Local pallidal and subthalamic activity predicts beta burst properties

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2) Department of Neuroscience, Faculty of Medicine, Technion Liliya Iskhakova,
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Beta oscillatory activity (13-30 Hz) is ubiquitous throughout the motor cortico-basal ganglia (CBG) network. Although an essential component of normal brain function, its association with anti-kinetic behavior and its pronounced expression in Parkinson's disease have identified it as a pathological marker. Previously, we and others have shown that a decrease in dopamine tone triggers a downward shift in beta frequency, alongside increased beta burst probability and duration. However, the intricate physiological mechanisms governing the emergence and modulation of beta oscillation properties, including frequency, amplitude, and duration, have remained unknown. In this study, we recorded from multiple nuclei along the CBG network under acute and chronic dopamine modulation and explored the relationship between dopamine modulation, neural firing rate, and the emergence and shaping of beta oscillations. Results revealed that single-cell firing rate and multi-unit activity can predict the frequency and duration of single-unit beta bursts, independent of dopamine tone. Notably, this association was more robust in the Globus Pallidus externus (GPe) and subthalamic Nucleus (STN) relative to the cortex. These findings highlight the role of GPe and STN in shaping beta oscillations and offer valuable insights for identifying pathological activity markers and improving treatments for conditions like Parkinson's disease.

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Cocaine Differentially Modulates Corticostriatal Pathways

Tomer Sheinfeld, *Hebrew University, ELSC*
Ami Citri, Hebrew University, ELSC

The striatum is the main input structure of the basal ganglia, integrating multimodal information from different cortical regions to facilitate motor learning. Different cortical regions, that carry different contextual information, are synapsing onto direct or indirect pathway neurons in the striatum – to guide the execution of appropriate behaviors. We sought out to identify dopamine's effect on different cortical projections to the striatum, and to isolate the contribution of different Corticostriatal pathways to the behavioral and cognitive effects of cocaine – a potent dopamine agonist. Using Pseudo-typed rabies virus, we have identified a population of indirect pathway projecting anterior-insula neurons that are affected by cocaine. In-vivo electrophysiology has revealed a dramatic effect of cocaine on the anterior insula and nearby primary motor cortex (M1). Focusing on striatum projecting cortical neurons, we observed an acute and long-term cocaine-induced decrease in activity of the insula, with increased activity in M1. Work in progress indicates that M1 projections to the striatum mediate vigor and motivation, while insula projections carry homeostatic and taste related information. Overall, our work highlights the behavioral relevance of different Corticostriatal pathways in the context of cocaine exposure, and elucidates their role in natural behaviors as well.

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Topographically-defined striatal circuits provide permissive drive to invigorate context-dependent actions

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The basal ganglia comprise several nuclei that together execute action selection. Understanding how individual actions are encoded within striatum and inter-connected basal ganglia circuitry is of crucial importance to understanding how reward guides our future actions, and to understanding the development of habits and addictions. Focusing on the lateral striatum, which receives homunculus-defined input from distinct sensorimotor cortices, and which is subdivided according to its body-region defined cortical input connectivity, we ask how individual actions are selected. To do so, we use a combination of optogenetics and fiber photometry calcium imaging. We find that body-part related action categories are encoded by striatal domains embedded in distinct connectivity-defined basal-ganglia loops. Simultaneous co-activation of distinct striatal subregions produces body-part composite actions. Finally, within any action category there doesn't seem to be a deterministic encoding of any distinct action (e.g. bite vs. lick). Rather, striatal activity seems to provide a permissive drive which invigorates multiple related actions within a body-region category, and the context in which the animal is located provides additional information which is important for choosing the exact action within the action category.

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Topic 18

Neural coding

Population-level coding of natural stimuli reveals the inter-areal organization of the mouse visual system

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Traditional techniques are limited to the recording of only a few neurons at a time. Therefore, classical studies of the visual system focused on studying responses to simple synthetic stimuli (e.g., moving gratings) which could be easily interpreted. While the scientific contribution of such studies is undeniable, it is unclear how suitable this reductionist approach is for understanding the processing of rich and ethologically relevant natural stimuli. Recent technological advances allow simultaneous recordings of many individual neurons, opening the door to complementary data analysis methods. Here, we analyzed large-scale optical and electrophysiological recordings of tens of thousands of neurons from six visual cortical areas in hundreds of awake-behaving mice that were presented with a wide battery of both natural and artificial stimuli. By focusing on the population-level organization of neuronal responses to natural stimuli, we reveal unique coding properties for each visual area that were not apparent when using simple synthetic stimuli. The functional differences were stereotypical across individuals, conserved across different types of natural stimuli, and consistent under fundamentally different analytical approaches. Importantly, the uncovered inter-areal organization of the visual system did not follow a simple feedforward hierarchy suggested by previous studies that used more traditional approaches.

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Representational Similarity Analysis as a generalizable function for image coding

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Representations in the brain are neural configurations encoding, storing, and interpreting stimuli (Marr, 1982), often studied via fMRI. Representational Similarity Matrices (RSMs) store Pearson correlations between stimuli representations, allowing comparison through Representational Similarity Analysis (RSA) (Kriegeskorte, 2008). RSA compares representations across subjects in fMRI experiments and between subjects and computational models, using brain activations from fMRI compared to artificial neural network outputs. fMRI data are also used for image reconstruction via Encoder-Decoder models (Gaziv et al, 2022). This study utilizes the NSD fMRI dataset (Allen et al., 2022) to examine the stability of image representations across brains, considering factors like repetition, voxel selection, and image-specific effects (Roth et al, 2023).

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Mesoscale dynamics of cell resolution cortical activity across brain areas in goal-directed behavior

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Goal-directed behavior requires the coordinated activity of sensory and motor areas across the brain. Recent advances in large-scale neural recordings allow studying brain-wide dynamics during behavior at cellular resolution. We used mesoscale calcium imaging to record the activity of up to ~30,000 neurons simultaneously (~1,000,000 neurons total) from over 10 cortical areas while mice performed a novel goal-directed naturalistic behavior. The behavior consisted of multipositional tongue-reaching movements to a target to obtain a water reward, with the target presented on a grid (typically consisting of 4x4 possible target positions) in front of the mouse's face. This behavior, which does not require training, allowed studying neural activity simultaneously across multiple cortical regions before neural activity is shaped by learning a specific task. Our analysis revealed a distinct task-related representation in different cortical areas, which evolved across time in some of the areas. Taken together, our results demonstrate a distributed yet specialized neural representation of task-related activity across the cortex during naturalistic goal-directed behavior.

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Internal strategies govern frontal or posterior brain-wide networks

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Sensory integration in the cortex is central to understanding the neural mechanisms of cognition. To further this understanding, we turned our focus to the whisker system of mice, drawing inspiration from the two-stream hypothesis in primates' visual system. We hypothesized similar 'what' and 'where' pathways diverging from the Barrel Cortex (BC). Using wide-field calcium imaging and body cameras, we examined brain activity as mice performed texture discrimination ('what') and location identification ('where') tasks. Our results challenge the idea of distinct 'what' and 'where' pathways in the whisker system. Instead, brain activity was driven by behavioral strategy: anterior areas were activated during active trials, and posterior areas during passive trials, regardless of task type. We identified anterior and posterior subnetworks extending from the cortex to the thalamus. A multiple linear model revealed that the anterior subnetwork correlated with movement-related variables, while the posterior subnetwork was influenced by internal states, such as strategy, history, and success. Additionally, the first learned task had a lasting effect on information processing in posterior areas, suggesting that past experiences shape internal states and problem-solving strategies. In conclusion, our findings reveal that brain processing streams are governed not only by external variables but also by internal strategies, providing new insights into how brain function is regulated.

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Unsupervised learning reveals stereotypical population activity patterns in the insular cortex

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Yoav Livneh, Weizmann Institute of Science

The insular cortex is involved in bodily homeostasis, emotions, and cognition, yet little is known about how information is represented by its neuronal populations. We developed an objective method to study neuronal population activity patterns in mice performing a sensory discrimination task for food or water rewards across different physiological need states. Our analyses revealed that the collective population activity patterns in the insular cortex, often referred to as the neuronal manifold, was remarkably consistent within and across mice. Our approach identified which subset of behavioral measurements contributed to the neuronal manifold, and which did not. Furthermore, we examined the dynamics of the neuronal manifold within the behavioral tasks, and revealed a distinct activity pattern during rewarded trials, which enabled us to reliably predict trial outcomes across days, across different mice, and across different mice with different physiological needs. Importantly, comparing task-structured goal-directed behavior with self-paced free consumption behavior, we found that the distinct reward pattern reflects task-dependent reward anticipation, and not behavioral action or taste. Our approach provides insights into information processing mechanisms of the insular cortex and introduces a novel approach for analyzing neuronal population data.

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Functional organization of the cognitive map for naturalistic reaching behavior in the motor cortex

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Goal-directed behaviors involve coordinated activity across neurons representing different cognitive variables that guide the appropriate action selection. Here we used a novel naturalistic behavioral paradigm that does not require pre-training, which allowed studying the underlying neural activity from the very first day of behavior. This paradigm involves tongue-reaching movements towards multiple target-positions, followed by a variable reward outcome. The target was presented on a grid (typically consisting of 4x4 possible target positions) in front of the mouse's face. We used calcium imaged to record neural activity in the anterior lateral motor cortex (ALM) – an area that plays a crucial role in sensory-guided licking planning and execution in mice. Unsupervised clustering of ~100,000 ALM neurons revealed organized neural activity, encoding movement timing and reward outcome for different target positions. Analysis of interactions between neurons in different clusters suggested functional coupling between neurons with shared response profiles during spontaneous activity. Removing shared components reveals increased functional coupling of reward-modulated neurons that respond late after movement and inhibitory interactions between neurons with opposite tuning. Our results suggest that the network of motor cortex neurons of naive (untrained) mice encode a structured cognitive map for goal position, movement time, and reward outcome. With experience, networks reconfigure with a redistribution of reward-modulated neurons and an increase in functional coupling between neurons of similar tuning.

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Prefrontal representations of social information and complex group dynamics

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The medial prefrontal cortex (mPFC) is strongly linked with social cognitive functions. However, how mPFC neurons process and represent social information and coordinate complex social interactions is only partly understood. We used wireless head-mounted neural loggers and wireless optogenetics to silence and/or electrophysiologically record 5,516 mPFC neurons in 17 groups of three or four (59 total) outbred male mice freely-interacting an enriched environment. Single-unit tuning curves showed that mPFC neurons represent both the subjects' and the other group members' location, 3D posture and movement kinematics, in the past, present, and future. Rigorous analysis showed that these neurons represent the others' behavior per se, beyond what could be explained by the subjects' own behavior. Moreover, these neurons represent the identity and social rank of the other group members, beyond what could be explained by the behavioral content of the social interactions. Finally, presenting the subjects with odor stimuli that represent individual mice in a highly-controlled, pseudo-randomized design demonstrated directly that these neurons represent the familiarity, social rank, and identity of the other group members per se. Taken together, this study enhances our understanding of how mPFC neurons represent both who one interacts with and what behaviors the social interaction includes.

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Long-term stability of mental representations of natural stimuli in humans

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Michal Ramot, Department of Brain Sciences, Weizmann Institute of Science

Recent advances in analysis approaches to neuroimaging data have enabled the examination of neural patterns of activation in human subjects. These patterns are meaningful and contain more information regarding the perception and mental state of the subject than the activity of individual voxels. Although much effort in the field has been made to characterize the neural patterns that correlate with specific stimuli or mental states and decode them, the understanding of how the neural representation of a specific perceptual experience evolves over time in humans is still lacking. Mouse studies have shown that although there is a time-dependent change in the population activity for any given stimulus, the structure of relationships between population activity patterns remains stable over time. To investigate this phenomenon of representational drift in human participants, we collected longitudinal high-resolution functional imaging data using 7T fMRI, with multiple repetitions of the same natural stimuli in multiple scanning sessions. We then performed a within-subject analysis to examine the stability properties of the population activity in response to repeated presentations of the same stimulus within a session and between different scanning sessions, as well as the nature of the relationships between different activation patterns. We will present preliminary results that explore the differences and similarities between multiple repetitions of the same naturalistic stimulus within individuals.

Topic 18

Neural Excitability, Synapses, and Glia: Neurotransmitter Release

Transfer RNA fragments sustain botulinum-intoxicated neurons viability by suppressing ferroptosis

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Botulinum neurotoxins (BoNTs) induce transient muscle paralysis via the blocking of cholinergic signaling in muscle-interacting neurons, but how these neurons maintain viability under BoNT/A intoxication is yet unknown. Here, we report that transfer RNA fragments (tRFs) that predictably target numerous cholinergic mRNAs showed up-and down changes in BoNT/A

intoxicated human neuroblastoma cells which also occurred in the sub-liminal gland of botulinum-intoxicated rats. Notably, 20% of those reactive tRFs carried a shared 11 nucleotides motif targeting the poisoning-declined cholinergic/pro-apoptotic UNC5B transcript. Moreover, pulldown experiments of the most highly expressed tRF tDR-1:31-Lys-TTT-3-M2 identified as its target the RNA-binding protein HNRNPM, known to induce the ferroptosis cell-death pathway. Correspondingly, HNRNPM protein levels declined 48hr post-intoxication, by that time fatty acids and arachidonic acid accumulation in poisoned cells accompanied with suppressed ferroptosis-hub transcripts to sustained neuronal viability. Together, these findings offer a novel route for maintaining neuronal viability under BoNT/A intoxication and predict possible therapeutic solutions for neuromuscular chilinergic disorders.

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Topic 19

Neural Excitability, Synapses, and Glia: Receptors and channels

Comparative analysis of channelrhodopsins for axonal projection stimulation

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Recent advancements in optogenetics have significantly enhanced our ability to manipulate neural systems with precise temporal and spatial control. This is achieved through the use of light-sensitive ion channels, which serve as either excitatory or inhibitory tools for light-driven neuromodulation. A wide range of channelrhodopsins is now available, each with distinct characteristics such as response latency, rise time, decay time, and peak photocurrent amplitude. However, this diversity introduces a critical challenge: selecting the most appropriate channel for a given experimental application. To address this issue, we characterized five channelrhodopsins with diverse functional characteristics: vfChrimson, ChrimsonR, Chronos, ChRmine, and CoChR. We first compared their function in dissociated neuronal culture, and then focused on their suitability for stimulating long-range neural projections using whole-cell electrophysiology in acute brain slices. We evaluated each construct based on its ability to achieve reliable, repetitive stimulation without causing excessive vesicle depletion, a common limitation for sustained neuromodulation. Our findings reveal the strengths and limitations of each construct, providing essential insights that guide the selection of the most suitable optogenetic tools for specific experimental goals. Through these carefully-controlled experimental comparisons, our work aims to refine optogenetic tool selection, ensuring more accurate and reliable outcomes in neuroscience research.

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Topic 20

Neurodegenerative disorders and injury: Alzheimer's Disease and Other Dementias

THALAMIC NUCLEUS REUNIENS REGULATES RESILIENCE TO SYNAPTIC & COGNITIVE FAILURES IN ALZHEIMER'S MODEL

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Objectives What mechanisms confer cognitive resilience to Alzheimer's Disease (AD)-related pathology? Resilience is principally expressed as a lack of dementia throughout lifespan in a subset of people with AD pathology, and as a long presymptomatic phase in AD patients. Here, we describe a neural circuit mechanism by which anesthesia dampens resilience to cognitive decline in AD. Results We show that CA1 pathophysiology emerges during anesthesia at the transcriptional, electrophysiological and behavioral levels, disrupting working memory in cognitively unimpaired AD-model mice. Anesthesia induces CA1 hyperexcitability, driven by inputs from the thalamic nucleus reunions (nRE). Indeed, tonic deep brain stimulation of the nRE (tDBS-nRE) restored state-dependent CA1 firing rate homeostasis and excitability and prevented further impairments of nRE-CA1 synaptic facilitation and

spatial working memory. Furthermore, tDBS-nRE, started during prodromal disease stage, mitigated age-dependent working memory decline.

Conclusions These findings highlight the nRE as a central node of functional resilience, suggest that anesthesia unmasks pathophysiology during prodromal disease phase and emphasize the clinical promise of DBS in conferring resilience to AD-pathology by restoration of circuit-level homeostasis.

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Investigating the Effects of HBOT on Cognitive Function and Neural Activity in 5xFAD mice

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Hyperbaric oxygen therapy (HBOT) includes administration of pure oxygen at high atmospheric pressure. HBOT is used on humans for several pathologies, mostly diving & radiation injury, and was recently shown to promote Aβ plaque clearing in 5xFAD mice (a transgenic Alzheimer's model). However, no neurological improvement was shown to be associated with HBOT yet. This study aim to investigate the effects of HBOT on both natural behavior that involved cognitive task and neurological function in 5xFAD and wild-type (WT) mice. Cognitive function will be assessed using Meister's Maze, a complex navigation task that measures spatial learning and memory. A separate group of WT and 5xFAD mice, expressing the fluorescent Calcium marker Thy1GCaMP, will undergo craniotomy (a surgical procedure in which a 3-mm opening is made in the skull) and shall be imaged using 2-photon microscopy to assess changes in neural activity after HBOT. This will allow to determine whether HBOT significantly improves cognitive function in both WT and 5xFAD mice, and if it lowers oxidative stress in the brain tissue of 5xFAD mice – thus providing insight into the potential use of HBOT as a treatment for Alzheimer's disease, as well as for cognitive decline in healthy individuals.

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The neuronal and peripheral immune response to sickness odor

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The extracellular matrix (ECM) plays an intricate role in brain structure and function. A specialized ECM structure, Perineuronal nets (PNN), mainly form around Parvalbumin GABAergic interneurons (PV cells), providing a protective shield, regulating activity, and contributing to synaptic stability and homeostasis. PNN loss has been reported in patients suffering from Alzheimer's disease (AD), as well as in a recent paper which also suggested that PNN loss is mediated by microglia. I set here to test this unexplored phenotype in a humanized model of the disease based on the apolipoprotein E4 (apoE4); the most prevalent genetic factor for AD. apoE4 had led to an early complex PNN phenotype; it decreased PNN density in the CA1 and Subiculum and increased PNN intensity in several brain regions. These events could affect plasticity and lead to synaptic impairments which are associated with the disease. To further dive into the study of PNN-microglia interactions, I have implemented a first-of- its kind approach to simultaneously image PNN and microglia in- vivo under two-photon microscopy. I share here preliminary results from this novel approach.

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DEVELOPING GENETIC TREATMENT OF NMDA RECEPTOR MEDIATED DISEASE BY TOXIN-LIKE PEPTIDE EXPRESSION

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Given the accumulating evidence regarding the roles of synaptic vs. extra-synaptic NMDAR in brain pathologies, we have begun to develop subtype specific antagonists for genetic treatment of NMDA mediated disease, focusing on Alzheimer's Disease. These antagonists have been previously genetically encoded in the lab, and we have enhanced them to target sub-cellular compartments, including the cell membrane, mitochondria, and secretory pathways. Preforming bioinformatical research on Alzheimer's disease multi-omics data, we look for cellular markers expressed in the disease state. These cellular markers will enable the focused expression of the genetic treatment limiting it to diseased neurons.

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UFMylation regulates proteostasis in C. elegans

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Hebrew University

The maintenance of protein homeostasis (proteostasis), by supervising the integrity of protein synthesis, folding, and the direction of misfolded polypeptide for degradation, is vital for cellular and organismal health. Malfunction of the proteostasis network (PN) leads to the accumulation of toxic protein aggregates which are tightly associated with the development of various late-onset neurodegenerative disorders. These include Alzheimer's disease (AD) and the group of polyglutamine (polyQ) expansion disorders such as Huntington's disease (HD). Post-translational modifications (PTMs) play key roles in proteostasis maintenance, and UFMylation, a ubiquitin-like PTM, is emerging as a significant modulator of these processes. Using the nematode Caenorhabditis elegans as a model organism, we discovered that UFMylation changes with age and is influenced by the insulin/insulin-like growth factor signaling (IIS) pathway, a key regulator of aging. Knocking down components of the UFMylation pathway, such as ufm-1 and uba-5, protected worms from the toxicity of Aβ3-42 and polyQ35-YFP, and slightly extended their lifespans. Interestingly, UFMylation knockdown reduced the levels of Aβ3-42 aggregates as well as of SDS-resistant polyQ35-YFP aggregates. Immuno-precipitation followed by proteomic analysis indicated that UFMylation is enriched in ribosomal, chromatin-remodeling, and cytoskeletal proteins, as well as in phagosome-related proteins which are involved in protein transport and clearance. An RNAi-based screen for some of the identified proteins revealed that the protective effects of UFMylation knockdown were closely tied to chaperones (HSP-1, HSP-90, SIP-1), the motor protein kinesin-19, and CAR-1,

suggesting these proteins are necessary for UFMylation's role in stress mitigation. To test how the reduction of UFMylation affects the transcriptomic landscape of worms that are challenged by Aβ3-42 proteotoxicity we performed an RNA sequencing experiment and found that UFMylation knockdown is associated with upregulation of genes that their products mediate immune defense and suppression of genes that are involved in reproduction, particularly in germline cells. Many of these transcriptional changes were linked to DAF-16 and HSF-1, both are well-established aging and stress responses controlling transcription factors, which are needed for the protective effect of UFMylation knockdown. These findings highlight UFMylation as a pivotal regulator of aging and proteostasis, involving chaperones, motor proteins, and transcriptional networks, and suggest its potential as a therapeutic target for neurodegenerative and age-related diseases.

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ODE-based Mechanistic Modeling of Alzheimer's Disease Progression

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Naomi Habib, ELSC, Barak Raveh

Alzheimer's Disease (AD) has emerged as a significant public health concern, prompting researchers to explore the intricate cellular communication within the brain during AD progression. Despite advances, much remains unknown about the cascade of cellular and molecular events driving the disease. Specific cell populations linked to AD have been identified, but their precise roles at different stages of the disease are yet to be understood. To bridge these knowledge gaps, we constructed a causal ordinary differential equation (ODE) model, describing the dynamics of classic disease pathologies throughout its progression and the contributions of distinct cell populations and risk factors. Employing a Bayesian approach, we optimized model parameters using a dataset of single cell RNA profiles from 424 aged human brains. Our goal is to comprehensively comprehend each cell population and risk factor's causal influence on AD's dynamics. Our research particularly emphasizes the impact of risk factors, such as ApoE4 genetic risk, age, and sex, on AD progression. By investigating the model's properties, we hope to shed light on cellular pathways driving the disease and identify potential therapeutic targets. This study holds promise for advancing our understanding of AD's complexities and guiding future treatment approaches.

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Does pregnancy with a Down Syndrome fetus promote maternal Alzheimer's Disease?

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Down Syndrome (DS), which results from a trisomy of chromosome 21 (Hsa21), is the most prevalent genetic cause of intellectual disability worldwide. Hsa21 contains genes linked to Alzheimer's disease (AD)-related pathology, including the amyloid

precursor protein (APP), of which the neurotoxic Amyloid-β (Aβ) peptide is cleaved from, causing early-onset AD-related neuropathology in DS individuals. An alarming association was previously reported between pregnancy with a DS-affected fetus and a 5-fold increased risk of maternal late-onset AD (LOAD), compared with pregnancies with fetuses with other forms of intellectual disability. However, the causative link between pregnancy with a DS fetus and maternal LOAD is yet to be established. We hypothesized that during pregnancies with a DS fetus, APP-related factors are transferred from the fetus to the mother, affecting the maternal cognitive abilities. To this end, wild-type female mice were mated with human APP-expressing mouse strains for 4 consecutive pregnancies, mimicking pregnancy with APP-overexpressing fetuses, as occurs in DS. Indeed, following these pregnancies, we have observed fetal human APP-related DNA, mRNA, proteins, and cells in the maternal brains and peripheral tissues, which resulted in maternal cognitive decline. These data suggest a mechanism by which pregnancy with DS fetus adversely affects maternal cognitive decline.

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COMPROMISED BRAIN VASCULATURE IN THE PROGRESSION OF ALZHEIMER'S DISEASE-LIKE PATHOLOGY

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Alzheimer's disease (AD), involves the accumulation of misfolded proteins, neuronal loss, and progressive cognitive decline. Amyloid-beta plaques and tau tangles disrupt cellular function and induce chronic inflammation. Although changes in blood-brain

barrier (BBB) integrity are linked to AD, the mechanisms underlying these changes remain unclear. This study aims to elucidate the mechanisms by which BBB dysfunction contributes to AD pathology and neuroinflammation in a mouse model of AD. Young and old 5xFAD mice (2-3 or 18-24 mo) and their littermate controls were injected with a small molecular-weight tracer (TMR-Biocytin~ 870 Da) testing BBB permeability. Then, mice were anesthetized, perfused and brains were extracted and processed for immunohistochemistry analyses. Using the imaging software IMARIS, cortical and hippocampal areas were analyzed. Compared to young 5xFAD mice and littermate controls, old 5xFAD mice showed no difference in the expression of the endothelial marker PECAM1. Nevertheless, we observed a decrease in the tight-junction protein Claudin-5, which was colocalized and normalized to endothelial marker PECAM1. Additionally, TMR-biocytin tracer assay demonstrated increased leakage through brain vessels in cortical areas of old 5xFAD mice, especially in regions with increased Aβ plaque load. Our results demonstrate a link between AD pathology and BBB changes, likely linked to neurotoxic inflammation. Understanding these pathways may uncover therapeutic strategies to mitigate BBB dysfunction and slow AD progression.

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The role of the brain-spleen circuit in the control of symptom onset in Alzheimer's disease

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A bi-directional crosstalk between the brain and the immune system is pivotal for healthy brain function. For example, the locus coeruleus (LC), controls the splenic nerve via release of norepinephrine which impacts the activation, maturation, and migration of immune cells. Here we hypothesized that this communication protects Alzheimer's disease (AD) brains from disease escalation. In a mouse model of AD (5xFAD), we found that LC-spleen communication is impaired in an advanced stage of the disease. However, when we experimentally impaired this communication the disease manifestation speedily progressed. Single-cell RNA-seq of immune cells in the spleen and brain, of sham relative to denervated 5xFAD mice, revealed downregulation of monocyte expressing homing markers, in the denervated mice. In the brain, we uncovered a reduction of monocytes homing to the brain and a

reduction in the disease-associated microglia in the denervated AD mice. Moreover, we found a strong shift in the signaling networks between microglia, monocytes, and macrophages in the brain after denervation, suggesting monocyte-dependent microglia activation in early-stage AD. These results underscore the brain's role in controlling innate immunity and the impact of monocytes on the state of microglia and the pathophysiology of AD, highlighting the dysfunction of the brain-spleen axis as a key player influencing AD progression.

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THE LONG-TERM EFFECT OF Δ9-TETRAHYDROCANNABINOL IN 5XFAD FEMALE MICE MODEL

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Objective: Current Alzheimer's disease (AD) treatments are limited, highlighting the need for innovative therapies. Δ9-Tetrahydrocannabinol (THC), cannabis' psychoactive component, usually associated with cognitive deficits, has demonstrated neuroprotective traits in ultra-low doses (ULD-THC). Our lab found that a single ULD-THC administration improved cognitive deficits in 5xFAD AD mice over three weeks. The current study investigates the single ULD-THC injection's long-term effects on AD-related cognitive decline and AD biomarkers in female 5xFAD mice (AD's prevalence is nearly twice in females).

Method: Six-month-old female 5xFAD and their wildtypes received a single ULD-THC (0.002 mg/kg) or saline injection. Behavioral tests assessing learning and memory occurred one- and 4.5-months post-treatment. Post-behavioral analyses, hippocampus, prefrontal cortex, and amygdala tissues were collected for quantitative PCR evaluation of AD biomarkers, neuroinflammatory markers, and neurotrophic factors.

Results: Consistent with previous findings, ULD-THC improved spatial memory in AD mice 1.5 months post-treatment. At 4.5 months, untreated wildtype mice outperformed untreated AD mice in Morris Water Maze, but treated AD mice performed similarly to wildtypes, indicating mild long-term effects. ULD-THC-treated AD mice showed reduced AD biomarkers and mitigated changes in neurotrophic markers, especially in the amygdala.

Conclusions: The findings suggest ULD-THC's potential in AD intervention, particularly targeting neuronal mechanisms.

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Dynamics of Neuronal Reprogramming Along the Alzheimer's Disease Cascade

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Alzheimer's disease (AD) is a progressive neurodegenerative disorder. Previous work revealed two distinct trajectories of coordinated changes across glial cells, one leads to AD and the other to alternative aging. Yet, despite the known neuronal damage, it is unclear at which stage and how neuronal cells are involved in this unique cellular cascade leading to AD. Here we charted the diversity of expression programs in the DLPC region from snRNA-seq profiles of ~1.68 million cells of 437 aging individuals by Topic modeling approach. In neuronal cells, we captured subtype-specific and general expression programs and uncovered a coordinated change in the expression programs in all neuronal subtypes along the AD trajectory, including downregulation of genes related to synaptic functions and up-regulation of stress genes and metabolic functions. Interestingly, this transcriptional change occurs at an early disease stage, before signs of cognitive decline or accumulation of the neurofilament tangles pathology. Moreover, these changes are coordinated with microglia shift to a disease state, and both are unique to the disease and not found in natural brain aging. Overall, our results position changes in neuronal functions among the first steps along the sequence of events leading to AD.

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Altered tRNA fragments in Alzheimer's disease reflect cognition differences

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Alzheimer's disease (AD) spreads throughout the brain, largely causing tissue alterations in the cerebral cortex and hippocampus. In patients at advanced AD stages, medical treatment is limited to palliative acetylcholinesterase inhibitors that may elevate acetylcholine levels but cannot slow down disease progression. However , small non-coding RNAs (sncRNAs) including microRNAs and the recently re-discovered tRNA fragments (tRFs) may alter gene regulation in the affected AD brains but have not yet been considered as AD therapeutics. To address this issue, we subjected inferior temporal gyrus tissues from AD patient brains and matched controls to small RNA-sequencing and analysed the data. Intriguingly, 5'-half tRFs known to be produced under cellular stress and accumulate in neuronal stress granules emerged as significantly upregulated in the AD tissues of both men and women patients and complementary to numerous cholinergic transcripts. Inversely designed synthetic sequences to such tRFs may block their activities, opening a possible new direction for designing potentially effective AD therapeutics.

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Novel Method for Objective Quantification of Apathy in Cognitively Normal Individuals at High Dementia- Risk

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Objectives: Apathy, which predicts cognitive decline and is associated with Alzheimer's Disease, is typically measured subjectively but may benefit from objective methods. Aims: Create objective tools to measure emotional and cognitive apathy.

Methods: We studied 82 middle-aged individuals with a family history of Alzheimer's. We used objective measures of gaze and autonomic nervous system (ANS) responses to emotional stimuli in a VR environment, and assessed cognitive effort through tasks. Subjective measures included the Apathy Motivation Index (AMI) and the Apathy Evaluation Scale (AES).

Results: Participants averaged 63.2 years old, with 52% women. AMI scores were below cutoffs for moderate and severe apathy. Higher self-reported apathy, especially low Social Motivation (SM), correlated with less variation in galvanic skin response and lower task engagement. Informant-reported apathy was linked to longer gaze fixation on aversive stimuli.

Conclusions: Objective measures of ANS and gaze reactions in VR, combined with cognitive effort tasks, may better capture subtle apathy than traditional questionnaires.

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Autophagy dynamics and regulation in neurodegeneration

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Neurodegeneration is characterized by protein aggregation, synaptic dysfunction, and eventual neuronal loss, often diagnosed in late stages when irreversible damage has occurred. Therefore, Early detection is critical for developing preventive strategies. Autophagy, a homeostatic recycling pathway, is essential for protein degradation. As such, it plays a pivotal role in neurodegenerative diseases, suggesting therapeutic potential through its augmentation. Our hypothesis states that in the early stages of neurodegeneration, before obvert neuronal dysfunction, aggregation of proteins leads to early synaptic upregulation of autophagy. Augmentation of this process over time leads to a failure point, resulting in structural and functional synaptic deficits. Here, we describe a novel way of monitoring autophagy in vivo using a two-photon fluorescence lifetime imaging microscopy (2pFLIM) sensor, designed to report pH-dependent autophagy flux. This allows for quantitative and longitudinal imaging of autophagy dynamics in intact cortical circuits. We applied this biosensor to monitor autophagy dynamics in a Tauopathy mouse model of neurodegeneration, in which Tau is mutated in P301S. We focus on early pre-symptomatic stages, where we performed in vivo imaging over time to identify critical time points in which autophagy dysregulation occurs at dendrites and synapses, were Tau forms initial tangles. We will further use this approach to identify the precise temporal and spatial dynamics of synaptic autophagy failure, which will be used to define an early marker of neurodegeneration and predict neuronal dysfunction onset. Our findings may advance early diagnosis of neurodegeneration and further used to test and advance early therapeutic avenues.

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The Role of Neuroinflammation and TrkB in Stress-Accelerated Alzheimer's Pathology in Mice

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While most Alzheimer's (AD) studies focus on the cognitive aspects of the disease, less focus is given to affective symptoms. In this study, we investigated the long-term consequences of exposure to chronic stress. 5xFAD AD model mice were exposed to Unpredictable chronic mild stress, and cognitive and emotional aspects were examined at 3 time points (up to 4 months after exposure to stress). We found that exposure to chronic stress exacerbates neuropathology in the 5xFAD mouse model in adulthood, accompanied by changes in the neurotrophic system. In-vitro, we show that corticosterone impairs the ability of microglia to uptake Aβ and reduces microglial activation. To conclude, our study shed light on mechanisms through which chronic stress might contribute to the onset and advancement of Alzheimer's disease symptoms.

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Assessing Sex Differences in Pathology in AD Mouse Model

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Background: Alzheimer's Disease (AD) is the most common form of dementia in the world, and nearly 2/3 of AD patients are females. Astrocytes are essential brain cells supporting neural metabolism and function. We previously reported that aged astrocytes (1) show impairment in supporting neuronal growth and clearance of beta amyloid in AD mouse model. Recent reports suggest potential sex differences in astrocyte activity (2).

Objective: To assess the effect of age on sex differences affiliated with astrocyte activity in mouse model of AD.

Methods & Results: Our methods include a transgenic mouse model in which we induce cellular senescence in astrocytes in background of 5xFAD mice. These mice were evaluated with cognitive behavioral tests and then sacrificed for biochemical, molecular biological, and histopathological assessments. In our preliminary results, we found sex differences both in behavior and molecular levels suggesting specific pathways that are affiliated with disease progression.

Conclusions: Our results may lead to an increase in understanding sex differences affiliated with AD toward potential new targets for personalized medicine. Bibliography: 1. Iram T et al, J Neurobiology of Disease, 2016 2. Gozlan E, Lewit Cohen Y, Frenkel D, 2024

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TARGETING METABOLIC CHANGES IN AGED ASTROCYTES IN ALZHEIMER'S DISEASE

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Scientific background Alzheimer's disease (AD) is one of the most common forms of dementia. One of its risk factors is aging. We have previously reported that aged astrocytes show impairment in their ability to support neuronal cells1. We reported a link between impairment within astrocytes metabolic activity2 to hyperphosphorylated TAU3. Objective We hypothesize that senescent astrocytes will show impairment in supporting neuronal cells and in clearance of Aβ. Methods and Results We induce astrocyte cellular senescence (CS) in 5xFAD mice and assess the effect on cognitive behavior, brain metabolism and pathology. To assess cognitive impairment, we assess their behavior monthly using Nesting and Y-maze. At 6 months mice were sacrificed and were assessed biochemically and histologically for disease pathology markers. We discovered that induction of senescence in those mice accelerates pathology and impairs brain metabolism. Conclusion This research would not only contribute to our understanding of Alzheimer's disease but also hold implications for the development of anti-neurodegenerative drugs by identifying pathways ripe for therapeutic intervention. References 1. Iram, T. et al. Neurobiol Dis 96, 84–94 (2016). 2. Chen, W. et al. Proc Natl Acad Sci U S A 120, (2023). 3. Farfara, D. et al. J Neuroinflammation 20, (2023).

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Targeting Alzheimer's Disease with Multi-Cellular New Chemical Entities

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This study aims to identify and evaluate new chemical entities (NCEs) with multicellular properties as potential countermeasures against damage induced to key neurovascular unit (NVU) cells in Alzheimer's disease (AD). We hypothesize that the NCEs can act as potent anti-AD drugs, preserving NVU functions such as blood-brain barrier (BBB) permeability, microglial phagocytosis, and neurite integrity under AD-like conditions. Experiments were conducted on human brain-like endothelial cells (BLECs), BV2 microglial cells, and differentiated SH-SY5Y neurons, which were exposed to AD-like conditions, including amyloid-beta (Aβ1-42) and tumor necrosis factor-alpha (TNFα) treatments, in the presence of increasing concentrations of various NCEs analogs. High-throughput live-cell imaging was performed over 24-72 hours, followed by viability analysis. Key cellular characteristics were assessed: BBB permeability, levels of tight and adherence junction proteins, microglial phagocytosis, and cytokine release. For neuronal degeneration - neurite length, branch points, and apoptosis were examined. Among the tested NCEs, several demonstrated significant protective effects, exhibiting multi-cellular beneficial properties. Cell death rates were significantly lowered in most cell types treated with these NCEs. Our findings highlight the potential of these NCEs as therapeutic agents for AD, meriting further investigation and clinical evaluation.

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COMBINATION TREATMENT OF SYSTEMIC A1 ANTI-TRYPSIN AND BLOOD-BRAIN BARRIER DISRUPTION INDUCED BY NON-INVASIVE LOW PULSED ELECTRICAL FIELDS (L-PEFS) FOR ALZHEIMER'S DISEASE

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Background: Alzheimer's disease (AD) is the most common dementia, associated with neurovascular dysfunction and pathology, such as Amyloid β (Aβ) protein deposits and blood-brain barrier (BBB) dysfunction. BBB dysfunction leads to reduced Aβ clearance, and neuro-inflammation, leading to cell death. Alpha 1 anti-trypsin (AAT) has anti-inflammatory properties, which can be used here. Therefore, in order to bypass the BBB, efficient BBB opening (BBBo) techniques would be needed.
Methods: A human BBB in vitro model was used to study Aβ aggregation and neuroinflammation. Additionally, we developed and tested a novel BBBo technique-low pulsed electrical fields (L-PEFs).

Results: In a cell free assay, AAT abolished Aβ1-42 aggregation. Using the BBB in vitro model, caspase-1 was shown to be activated by Aβ1-42, and AAT inhibited caspase-1 activation, reducing neuro-inflammation. Next, AAT+/-L-PEFs, in mice, was studied to determine efficacy of this BBBo. ELISA showed AAT (1.3ng AAT/mg brain tissue) in brains of all L-PEF treated mice, while sham mice had no AAT.

Conclusions: The BBBo (L-PEFs) allows AAT to enter, reducing Aβ and neuroinflammation. Combining a novel drug that targets the multiple entities of AD with an efficient and safe BBBo technology can lead to new and effective treatments for AD.

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EARLY BIOMARKERS IN ALZHEIMER'S DISEASE BY CREATING A SUPER-RESOLUTION SPATIAL GENOMIC MAP IN THE HIPPOCAMPUS

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Alzheimer's Disease (AD) is a devastating neurodegenerative disorder whose etiology is poorly understood and for which no efficient therapy exists. One key question is how cells respond to AD-related microenvironmental cues, for example, the toxic amyloid plaques. In this research we investigate whether cells, specifically neurons, change their molecular properties primarily in the areas in the hippocampus of 4 weeks old mice where Aβ plaques are expected to be developed. In my research, I use expansion sequencing (ExSeq). This new technology enables to resolve millions of RNA molecules in situ, i.e., in their original locations inside the tissue. I applied ExSeq to the hippocampal region, one of the first to be eventually affected with Aβ plaques, in a mice model of Alzheimer's Disease (5xFAD). ExSeq was utilized to create molecular maps of the mouse hippocampus, which allows detecting early changes in the molecular content of neurons in the hippocampus of 5xFAD mice. By sequencing 100 genes in situ, we analyze neuronal content with super-resolution and detect molecular changes in cells at the early stages of AD.

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Deciphering the mechanisms beyond the high risk for cognitive decline in Haptoglobin (Hp) 1-1 carriers in diabetes: an in -vivo study using humanized Hp mice

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With obesity levels rising, a significant rise in diabetes occurs in the world population. Diabetes is a major risk factor for developing Alzheimer's disease (AD), although the mechanisms beyond it are not clear. Since diabetes is strongly associated with vascular dysfunction, we and others explore the involvement of the blood-brain barrier (BBB) in the etiology of AD under diabetic conditions. Haptoglobin (Hp) protein responsible for the elimination of toxic free hemoglobin from circulation. In humans, two frequently occurring allelic forms of Hp result in three genotypes. The Hp2-2 genotype has been associated with various cardiovascular diseases. In contrast, our latest publications showed a cognition decline in diabetic people carrying the Hp1-1 genotype. By synteny between mice and humans, we hypothesized that under diabetic-like conditions, mice with the Hp1-1 genotype might develop more severe and faster cognitive decline than genetically modified mice with the Hp2-2 genotype. Our results emphasize that although DM1 and DM2 have common features such as hyperglycemia, they are very different diseases with different and complex peripheral and central nervous system (CNS) symptoms that need to be addressed accordingly in the context of risk management for better brain health.

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DISEASE-ASSOCIATED COMMITTED OPCS EMERGE AS SECRETORY CELLS SHAPING THE FATE OF ASTROCYTES IN EARLY STAGES OF ALZHEIMER'S DISEASE

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Alzheimer's disease (AD) is a progressive neurodegenerative disorder. Cellular changes across brain cell types preceding cognitive symptoms, suggest early molecular drivers of cellular changes might be potential therapies. By single-nucleus RNA-seq we profiled the cellular environment in an AD-amyloidosis mouse model, identifying coordinated transitions in glial cell types towards disease-associated states, including a new population of disease-associated committed oligodendrocyte precursors (DA-COPs). DA-COPs, predicted to be arrested at a transitional state between precursor and oligodendrocytes, are to serve as signalling hubs. Specifically, we predict BMP4 signalling from DA-COPs to drive disease-associated astrocytes (DAAs). Spatial transcriptomics showed co-occurrence of the rare COP cells with DAAs. In vitro, primary astrocytes exposed to BMP4 exhibited morphological changes and upregulated inflammatory and DAA genes, indicating BMP4 driving a transition into a diseased state. We confirmed DA-COPs state in present also in the ageing human brain and show BMP4-induced pathway in DAA-like human astrocytes. We suggest DA-COPs as early signalling hubs, accelerating astrocytes transitioning into a diseased state along amyloidosis progression via BMP4 signalling.

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New MRI quantifiers for mictrostructural analysis in AD

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Weighted MRI images, such as T1-weighted, T2-weighted, and proton density-weighted (T1w, T2w, and PDw), are frequently used in clinical neuroimaging and open-source databases for assessing brain structure. These images reveal macrostructural details but lack the physical meaning necessary for microstructural analysis. Quantitative MRI (qMRI), which includes relaxation rate parameters like R1 and R2, does provide microstructural information but is seldom included in large clinical databases due to its complexity. To address this gap, the ratio of T1w to T2w images is sometimes used as a proxy for microstructure and has shown links to Alzheimer's disease markers (Luo et al., 2019; Lim et al., 2023). In this study, we introduce three additional quantifiers that approximate qMRI maps, aiming to make qMRI insights accessible in clinical settings. By mathematically combining T1w, T2w, and PDw images, we estimate R1 and R2 values. Specifically, we find that T1w/PDw and T1w/ln(T2w) correlate with R1, while ln(T2w/PDw) aligns with R2. Using these quantifiers in the ADNI dataset, we observe significant differences in the hippocampus, amygdala, and entorhinal cortex across Alzheimer's clinical groups. This approach offers a way to harness weighted MRI for semi-quantitative MRI analysis in clinical Alzheimer's research.

Topic 20

Neurodegenerative disorders and injury: Movement disorders

ASSOCIATION OF REAL-WORLD WEARABLE MOBILITY MEASURES WITH PARKINSON'S DISEASE SEVERITY AND DISEASE PROGRESSION

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Background: Real-world monitoring using wearable sensors has enormous potential for assessing disease severity and symptoms in Parkinson's disease (PD). The aim of this study was to identify which real-world mobility measures reflect PD severity, evaluate discriminate ability and sensitivity to change compared to the clinical scale.

Methods: Multicenter real-world continuous (24/7) digital mobility data from 587 patients with PD and 68 healthy controls were collected using a data-logger adhered to the lower back. Machine-learning algorithms evaluated associations with the clinical scales. Binary logistic regression assessed discriminatory value and longitudinal data from a subgroup evaluated sensitivity to progression.

Results: Digital measures were moderately correlated with the clinical scale(r=0.50); with the majority of features reflecting activity quantity and distribution patterns. A model with 14 digital features accurately distinguished recently diagnosed patients with PD from controls (81.1%, AUC 0.87) and digital measures showed larger effect sizes than the clinical scale.

Conclusions: Real-world mobility measures show moderate associations with the clinical assessment, suggesting that digital measures capture different aspects of capacity and function. Digital mobility measures are also sensitive to early-stage disease and to disease progression, to a larger degree than the conventional clinical assessments, demonstrating their utility for clinical care and clinical trials.

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A NOVEL PERSONALIZED TARGETING METHOD FOR MR–GUIDED FOCUSED ULTRASOUND (MRGFUS) THALAMOTOMY

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The objective of this study was to evaluate a new method for pre-surgical planning in MR-guided focused ultrasound (MRgFUS) thalamotomy. Data from 50 patients (4 with Parkinson's disease and 46 with essential tremor) who underwent unilateral MRgFUS thalamotomy at Sheba Medical Center between 2018 and 2021 was collected. Among these patients, 33 underwent the procedure using traditional indirect targeting approach, while 17 underwent the MRgFUS procedure using the pre-planning personalized integrative novel analysis. The new model included an integration of direct and indirect targeting by delineating the ventral intermediate nucleus (VIM) and its associated fibers of the dento-rubro-thalamic tract (DRTT). The personalized integrative targeting system resulted in a lower incidence of sensory adverse effects and gait disturbance compared to the classical indirect targeting method. Moreover, using the personalized approach significantly fewer sonications and ablations were required, leading to reduced procedural time and patient discomfort. These findings suggest that the novel method enhances the accuracy of targeting and reduces adverse effects in MRgFUS thalamotomy. Additionally, it improves surgical efficiency by minimizing the number of sonications and ablations needed for optimal outcomes. These results hold significant promise for improving pre-surgical planning and enhancing patient outcomes in MRgFUS thalamotomy procedures.

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Genome-wide identification of aberrant alternative polyadenylation linked to TDP-43 pathology

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Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease marked by motor neuron loss, causing progressive paralysis and death without a cure. Approximately 90% of ALS cases are referred to as sporadic. A breakthrough in ALS research identified nuclear clearance and cytoplasmic aggregation of the RNA-binding protein TDP-43 in over 95% of ALS cases and nearly 50% of frontotemporal dementia (FTD) and Alzheimer's patients. TDP-43 is essential for RNA processing, including transcription, splicing, transport, and alternative polyadenylation (APA). Recent studies reveal TDP-43's role in preventing premature polyadenylation of the mRNA encoding stathmin-2, a vital protein for neuronal growth and regeneration. We employed 3'-end RNA sequencing to determine transcriptome-wide the extent of TDP-43's regulation of APA across various cell types and conditions, including neuronal cells edited to carry an ALS-causing mutation in TDP-43 coding gene, human iPSC-derived motor neurons with TDP-43 depletion or pathology, and ALS patient spinal cord sections. Analysis of APA events linked to TDP-43 dysfunction revealed shifts in polyA site selection, altering the 3' UTR length of pre-mRNAs, shortening or lengthening different mRNA target sets. We are currently investigating how TDP-43-related APA changes impact mRNA stability and localization in motor neurons, seeking early biomarkers and therapeutic targets for ALS.

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Topic 21

Neurodegenerative disorders and injury: Parkinson's Disease

EXPLORING SLEEP DISTURBANCES IN DRUG-NAIVE PARKINSON'S DISEASE PATIENTS

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Parkinson's disease (PD) is a neurodegenerative disorder characterized by motor symptoms such as tremors, rigidity, and bradykinesia. PD also involves sleep abnormalities that occur from the onset of, and even prior to, motor symptoms and worsen as the disease progresses. A major challenge is that PD patients typically receive drug therapy that affects dopaminergic signaling, likely affecting sleep irrespective of the disease. Only several studies investigated sleep in drug-naïve PD patients (dn-PD), suggesting that at least some sleep abnormalities are intrinsic to the disease. To further investigate this, we used high-density (256-channel) electroencephalography to study overnight sleep architecture and EEG sleep oscillations. We compared sleep in 30 dn-PD patients (H&Y stage 1-2, ages 65.4(7.2)) to 30 healthy controls (ages 64.7 (7.5)) and to 30 PD patients receiving drug therapy (H&Y stage 1-3, ages 64.9(10.9)). Patients underwent clinical and neuropsychological assessment (e.g. MOCA, motor evaluation (UPDRS)) and screening for potential sleep breathing abnormalities and RBD. Preliminary results show that dn-PD patients exhibit decreased REM sleep and increased latency to both REM sleep and NREM sleep, suggesting that PD is associated with disruptions in sleep architecture irrespective of medication. We are now investigating potential changes in specific features of EEG sleep oscillations.

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RNA Granule Alterations in Parkinson's Disease

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Processing bodies (PB) are one example of RNA granules comprising of mRNA translation regulators including initiation and silencing mediators and ribonucleoprotein particles. Additional types of RNA granules include stress granules (SG) and neuronal granules (NG) which enable a cell to maintain proteostasis during stress by prioritizing specific mRNA translation and facilitate a neurone's unique requirement of transporting untranslated mRNAs across distal locations including the dendritic synapse, respectively. These membranelles organelles are highly dynamic and form via lipid-lipid phase separation. Current understanding is lacking regarding their role in neurodegenerative diseases but there has been recent evidence suggesting that Parkinson's disease (PD) associated proteins such as alpha-synuclein, interact with PB or SG components. Therefore, this project hypothesizes that mutations driving pathological alpha-synuclein aggregation in Parkinson's disease (PD) can alter RNA granule dynamics and contents which can contribute to neurodegeneration. To investigate such, several beyond-cutting edge nanoscopic imaging modalities will be integrated, including expansion microscopy (ExM), spatial transcriptomics (ExSeq) and single-molecular localization microscopy (SMLM), specifically direct stochastic optical reconstruction microscopy (dSTORM). Therefore, a novel approach will be adopted to obtain a nanoscopic understanding of the transcriptomic and proteomic mechanisms occurring in ageing-related diseases, including PD, to facilitate the identification of new therapeutic targets.

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Unraveling the mechanisms of a-synuclein aggregation in models of Parkinson's disease

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The accumulation and aggregation of α-synuclein is a central element of Parkinson's disease (PD), but the molecular mechanisms responsible for these processes are not fully understood. Currently, there is no neuronal model that consistently shows α-synuclein aggregation in neurons. Previous neuronal models using toxins such as MPP+ or α-synuclein pre-formed fibrils have not been able to fully mimic the disease. We now sought to mimic and investigate in neurons the effect of various pathological conditions thought to influence PD, including oxidative stress and impaired blood supply. Several studies have shown that brain vasculature is significantly impaired in prodromal PD, suggesting that the supply of nutrients may also be impaired in early stages of the disease. In agreement, we found that withdrawal of amino acids from the culture medium promotes robust aggregation of a-synuclein in HEK293 cells and primary neurons. In HEK293 cells, aggregation of a-synuclein is limited and appears mainly as a 50 kDa form (a-Syn50). In neurons, the aggregation of a-synuclein upon amino acid starvation is more prominent and appears as a high molecular weight smear. This aggregation begins in the processes and progresses temporally into the soma of neurons. Expression of wild-type or disease mutant A53T aggregates upon amino acid starvation, suggesting that this effect may occur in both familial and sporadic disease. In addition, amino acid starvation promotes much less pronounced aggregation of other neurodegenerative disease proteins, including the wild-type and disease mutants tau and TDP-43. Moreover, upon amino acid starvation, aggregated

a-synuclein becomes SUMOylated. We also found that aggregation of a-synuclein in neurons is prevented by the addition of amino acids to a non-enriched medium, but once aggregation has started, the process is irreversible, even after the addition of amino acids. Finally, we do not observe robust aggregation of endogenous a-synuclein, suggesting that the decrease in amino acid support may represent an event secondary to the prior accumulation of a-synuclein in the brain. Understanding the mechanisms underlying α-synuclein aggregation in PD is critical for the development of targeted therapies. Our findings suggest that maintaining amino acid homeostasis may be important to prevent or slow the disease progression.

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Early Detection Platform for α-Synuclein Aggregates in Skin Biopsies of Parkinson's Disease

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a-Synuclein (aSyn) aggregation in the central nervous system has been associated with progression of Parkinson's Disease (PD) and is currently considered the main pathological hallmark of the disease. aSyn is found not only in the brain but also in peripheral tissue, such as innervated structures in the skin, which could provide a novel and minimally invasive method for PD diagnosis. The goal of this research is to characterise aSyn as a biomarker for PD in minimally invasive skin biopsies by optimising super resolution microscopy (SRM) imaging of αSyn aggregates in skin biopsies, creating a user-friendly cluster analysis platform, uniting various clustering algorithms and functions, and implementing a machine learning algorithm to correlate aSyn aggregates with patients' clinical status. The use of direct Stochastic Optical Reconstruction Microscopy (dSTORM), a form of single molecule SRM, allows to quantitatively analyse composition of aSyn aggregates and differentiate between

monomeric aSyn and aSyn aggregates at different stages of their formation. This high-resolution approach may allow us to identify and characterise early stages of aSyn aggregation. Preliminary analyses show significant differences in cluster properties between PD and control subjects and correlations between some cluster properties to several PD clinical parameters.

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The role of mitochondrial malfunction in the initiation/progression of Parkinson's Disease

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Atan Gross, WIS

Parkinson's disease (PD) is a multifactorial neurodegenerative condition, characterized by the loss of midbrain dopaminergic neurons and subsequently by impaired motoric and cognitive functions. α–synuclein (αSyn) aggregates clearly play a critical role in the initiation/progression of PD, however the importance and role of mitochondrial malfunction in PD remains unclear. Our hypothesis is that mitochondrial malfunction results in an increase in the formation of αSyn aggregates. To test this hypothesis, we established cell lines that stably express αSyn, and tested the effect of healthy and malfunctional mitochondria on the formation of αSyn aggregates. Our preliminary results show that healthy/functional mitochondria reduce the levels of αSyn aggregates, whereas malfunctional mitochondria increase the aggregate levels. Thus, αSyn may act as a surveillance factor for mitochondria well-being. Future studies focused on the functional relationship between αSyn aggregation and mitochondria function may shed new light on the actual molecular processes leading to the neuronal damage and degeneration responsible for the appearance and development of PD, which can possibly help diagnose the disease at earlier stages and provide potential new targets for therapy.

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CHARACTERIZING THE APERIODIC AND PERIODIC COMPONENTS OF THE STN ACTIVITY IN PARKINSON'S PATIENTS

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The present studies demonstrate that both local field potentials (LFP) and spiking (SPK) activity in the subthalamic nucleus (STN) are associated to Parkinson's disease (PD) symptoms. However, their relationship is elusive. We explore this by separating STN signals of 146 PD patients (encompassing 308 trajectories and over 25,000 recording sites) into aperiodic and periodic components and by whitening these signals using their corresponding aperiodic exponents. Our results indicate that the LFP aperiodic exponents resemble Brown noise () and are significantly higher than SPK aperiodic exponents (, White noise). Furthermore, the periodic oscillations of LFP are predominantly distributed in the high beta frequency domain while those of SPK are in both low and high beta domains. We also observed a downshift in beta oscillation center frequencies in SPK relative to simultaneously recorded LPF. This demonstrates that the STN synaptic input (LFP) undergoes significant modifications when transformed into STN output (SPK) of PD patients, and may explain the critical role of STN in PD physiology and STN-DBS (Beep Brain Stimulation of Subthalamic Nucleus) therapeutic efficacy.

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Identification of molecular signatures in peripheral autonomic neurons associated with Parkinson's disease

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Objective: Given that pathological signs of Parkinson's Disease (PD) are frequently observed in the peripheral autonomic nervous system (P-ANS), and exposure to environmental toxins has been linked to cases of PD; while no clear PD-associated molecular signatures have been identified, we aim to investigate dysregulated pathways related to PD in the P-ANS.

Methods: In this ongoing study, we tested whether peripheral autonomic neurons exposed to the neurotoxin rotenone exhibit PD pathological phenotypes. The P-ANS is modelled using induced pluripotent stem cells (iPSCs) derived from patients with young-onset PD and control subjects. iPSCs are utilized to generate autonomic neurons, which are then exposed to rotenone. Concurrently, transcriptome and proteome mapping of rotenone-treated and untreated control autonomic neurons are performed, comparing them to PD autonomic neurons.

Results: We identified novel perturbed targets from transcriptomics and proteomics analyses of rotenone-exposed neurons, validating our experimental design. Additionally, we succeeded in differentiating iPSC lines from sporadic young-onset PD patients into P-ANS neurons.

Conclusion: Our results will enhance our understanding of PD biology and contribute to the development of future therapeutic modalities. This research will assist to identify dysregulated genes that could serve as novel pathological targets for tracking early PD progression in the periphery.

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Impact of Parkinson's Disease on Motor Learning and Neuronal Network Dynamics in Mice

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Technion

Learning is a dynamic process which has been a longstanding focus in the neuroscience community. Parkinson's Disease (PD) is a degenerative condition in which the performance of learnt skills is impaired, and in some cases requires "re-learning". In this project we explore the effect of motor learning before and after onset of experimental 6-hydroxydopamine (6-OHDA) PD on the neuronal activity of mice learning and performing a lever-pull motor task. Specifically, we investigate network dynamics of dendritic signals recorded from the tuft of layer 5 pyramidal tract neurons of the primary motor cortex. We show that before the onset of PD, as animals learn to perform the task the neuronal activity becomes more statistically related to the motor movement. This transformation is also demonstrated at the network level where connectivity is gradually shifting from a beginner's configuration to an expert's one. Our analysis of data recorded after induction of PD by local injection of 6-OHDA to the ipsilateral striatum indicate that experimental PD disrupts the network organization associated with motor learning in the primary motor cortex as mice relearn the task the Parkinsonian network reorganizes to a new expert state where a smaller part takes part in the encoding of movement.

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Investigating oculomotor properties during locomotion in Parkinson's Disease and healthy adults

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Although Parkinson's Disease (PD) affects the motor system, not much is known about its effects on oculomotor (eye movement) control. Here we wish to examine this by analyzing eye movements measured in PD patients (4 females and 8 males, aged 67±8.7 with PD duration of 4-23 years) while on and off their medication and in age-matched control adults (4 females and 8 males, aged 75.5±5.4) while walking in a two meter wide corridor performing 90 and 180 degrees turns, wearing accelerometers of gait analysis system (APDM®) Further, their eyes were tracked by PupilLabs Core device. No medication-based influence or between-group differences were evident in cognitive levels as assessed by MOCA scores. Preliminary analyses show that PD patients' eye tracking data were assigned lower confidence scores such that more eye tracking data was determined as unreliable. In addition, in these preliminary results we find that medication affects data reliability and oculomotor behavior (e.g. during sharp turns). More elaborated analyses including examinations of data quality, ranges, and variance and the effect of medication on these measures will be presented.

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Assessing The effects of High Fat Diet on the Progression Rate of disease in Parkinson's Disease mouse model

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2- sagol school for neuroscience, Tel-aviv university

Scientific Background: Parkinson's disease (PD) is the second most common neurodegenerative disease, affecting motor skills and may lead to non-motor symptoms such as stress. Insulin regulates energy metabolism, facilitates glucose uptake, maintains neuronal balance, and influences neurotransmitter release. Dysregulation of brain insulin signaling is linked to neurodegenerative diseases, such as PD.

Objectives: To assess the effects of a high fat diet (HFD) on the development of behavioral impairment and brain pathology in a PD mouse model.

Methods and Results: Both males and females 3KL mice were fed from the age of 2 months (before the onset of the disease) until the age of 6 months when the pathology is well developed. We used the Y-maze, Grip strength, Catwalk, and nesting tests to assess the changes in behavior. We also assessed insulin activity and pathology. We discovered that HFD impaired insulin activity and was linked to accelerated clinical pathology in mice.

Conclusions: Our results suggest a link between HFD to neurological changes in PD and may identify new therapeutic targets for future medical intervention.

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Investigation of the effects of Emrusolmin (TEV-56286) on alpha-synuclein aggregation modulation in Synucleinopathies

Michal Broday, *Sagol School of Neuroscience*, *Ashery Lab, Neurobiology*

Synucleinopathies are neurodegenerative disorders characterized by the abnormal accumulation and aggregation of the synaptic protein, alpha synuclein (α-syn). In healthy conditions, α-syn plays a role in synaptic vesicle trafficking and neurotransmitter release through interactions with SNARE proteins. The irregular aggregation of α-syn can impair normal SNARE complex function, leading to synaptic dysfunction. Current treatments for synucleinopathies only address symptoms, leaving patients vulnerable to ongoing neuronal damage. Emrusolmin, a small molecule compound, has shown promise as an α-syn aggregation inhibitor by de-stabilizing early-stage aggregates, thereby depopulating toxic aggregates into smaller, non-toxic species. Thus, emrusolmin may offer a promising therapeutic strategy for patients with synucleinopathies. Our research aims to investigate the efficacy of emrusolmin in mitigating α-syn aggregation across various experimental models. To accurately study the accumulation and aggregation of α-syn, we utilize super-resolution microscopy imaging (direct Stochastic Optical Reconstruction Microscopy – dSTORM). Preliminary data in primary neuronal cultures expressing the a-syn A53T mutation revealed that emrusolmin reduced phosphorylated α-syn aggregates compared to untreated neurons. Changes in inner density, radius and number of a-syn molecules per aggregate were observed following treatment. These results support earlier studies and provide a foundation for further research into Emrusolmin's potential as a therapeutic agent in synucleinopathies.

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A psychophysics paradigm to detect proneness to formed visual hallucinations

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Amit Yelin The Gonda Multidisciplinary Brain Research Center Adam Zaidel The Gonda Multidisciplinary Brain Research Center

Formed visual hallucinations (FVHs) are a perceptual impairment where people see non-existent objects or animals. Because FVHs are subjective and transient, they are difficult to quantify using psychophysics experiments. Proneness to FVHs is typically measured using object recognition tasks with a limited number of stimuli (20~30 images) that can possibly be memorized. Thus, a larger set of stimuli is needed. Here, we created a set of 194 images, comprising 100 morphed objects and 94 chimerical animals. A small group of healthy participants rated the realness of those images. Their ratings aligned with CLIP (Contrastive Language-Image Pretraining) model realness labels. The set was then tested on 51 healthy participants online to establish a baseline for FVHs proneness. Hallucination proneness (self-report) was measured using the Cardiff Anomalous Perceptions Scale (CAPS). Participants with higher CAPS scores reported unreal images as more real ($p = 0.031$), an effect absent in control tasks for spatial perception and object naming. This suggests that FVHs are linked specifically to object perception rather than a general decline in visual perception. In future work, we will test whether these tasks can be used to measure FVH severity or for screening people diagnosed with clinical FVHs.

Topic 22

Neurodegenerative disorders and injury: Stroke and injury

IDENTIFYING TRACES OF DEMYELINATION CAUSED BY MICROINFARCTS THROUGH EEG INTERHEMISPHERIC COHERENCE

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1 School of Neurobiology, Biochemistry and Biophysics, Tel Aviv University, Tel Aviv,
2 Sagol School of Neuroscience, Tel Aviv University, Tel Aviv

Comprehending the consequences of demyelination and its influence on the brain following a vascular insult is important for understanding the process of neurological disorders. In this study, we employed electrocorticography (ECoG) as a method to investigate traces of demyelination in mice brain subsequent to single and multiple penetrating artery occlusion induced via the photothrombotic technique. ECoG recordings were conducted to compare changes in brain electrical activity pre and post-occlusion following several days, with a particular focus on interhemispheric coherence as an indicator of disrupted communication between brain hemispheres. ECoG data was collected during resting-state and sensory-evoked responses. Notably, reduced interhemispheric coherence was observed, signifying impaired connectivity between the two hemispheres due to demyelination. This was also confirmed by reduced power of high frequency bands like alpha and delta bands in mice with microinfarcts compared to the control group. The correlation between ECoG changes and reduced interhemispheric coherence sheds light on the impact of microinfarct(s) on brain electrical signaling and connectivity. These findings offer crucial evidence for understanding the functional consequences of vascular-induced brain injuries and provide a foundation for future investigations on microinfarcts and their implications for brain health and neurological disorders.

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THE EFFECT OF PUBESCENCE ON BRAIN CONNECTIVITY AND EXECUTIVE FUNCTIONS AMONG GIRLS WITH TRAUMATIC BR

Yael Golan1,2,3, Reut Raizman1,4, Moran Shectman1,2,3, Hadar Shapsa1, Galia Tsarfaty1,4, Neta Erez3, Jana Landa3,4, Tamar Silberg*2,3, Abigail Livny*1,4,5

Puberty is a crucial developmental milestone with physical, neurological, hormonal, and psychological changes. Investigating the influence of pubertal stage on recovery from pediatric traumatic brain injury (pTBI) is challenging, given the potential impact on brain reorganization and executive functions (EF). This study aimed to explore the link between pubescence, brain connectivity, and EF in pTBI females, compared to healthy controls. Nineteen pTBI patients and 30 healthy controls, aged 9-18, underwent MRI scans, EF tests, and filled a puberty questionnaire. Graph theory (GT) network analysis of diffusion imaging was conducted. An EF factor and binary pubescent score were computed. A multiple regression analysis was conducted to examine model's impact on EF variance. The EF factor was predicted by the model as a whole, by the GT measure of clustering-coefficient (CC) and injury group alone, but not by pubescent stage. However, interaction effects were found between pubescent and injury group and CC and injury group. Our findings suggest that developmental stage may play a crucial role in determining the impact of pTBI on EF in females. These findings shed light on the nuanced dynamics involved in EF impairment and have implications for personalized interventions and targeted rehabilitation strategies for individuals with pTBI.

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DECREASED HOMOTOPIC FUNCTIONAL CONNECTIVITY IN PEDIATRIC PATIENTS WITH TRAUMATIC BRAIN INJURY

Hadar Shapsa1,2, Reut Raizman1,3, Yael Golan1,4, Moran Shectman1,4, Neta Erez4, Jana Landa3,4, Galia Tsarfaty1, Tamar Silberg4,5, Abigail Livny1,3,6.

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5. Department of Psychology, Bar Ilan University, Ramat Gan, Israel 6. Sagol School of Neuroscience, Tel Aviv University, Tel Aviv, Israel

Introduction: Functional Homotopic Connectivity (HoFC), the synchrony in activity patterns between homologous brain regions, is a crucial aspect of resting-state functional connectivity (RsFC). In a prior study, we discovered reduced HoFC among adult TBI patients. We aimed to explore whether pediatric traumatic brain injury (p-TBI) patients exhibit a similar decrease in HoFC, which in turn may lead to disrupted RsFC with other brain regions.

Methods: Forty-five p-TBI patients from all injury severities and 45 age- and gender-matched healthy controls were recruited and followed for 6 months. Resting-state fMRI scans were conducted and correlations were computed between atlas-based regions and their counterparts on the opposite hemisphere.

Results: During the acute phase, p-TBI patients showed decreased HoFC in cingulate and temporal regions. Seed-based analysis revealed reduced RsFC between the right superior temporal and the left parsorbitalis, and the right pars opercularis. Additionally, p-TBI patients exhibited decreased FC between the left temporal pole and left superior parietal, and right insula.

Conclusions: These findings are the first to underscore the effect of pediatric brain injury on inter-hemispheric synchronization and suggest potential implications for cognitive decline and clinical outcomes.

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Unveiling Personality in Drosophila Melanogaster: Bridging Human Psychology with Insect Behavior

Hadar Pozeilov, Elia Dayan, Mali Levi, Oren Forkosh, Galit Shohat-Ophir

Bar - Ilan University

Individual differences, also referred to as personality, are a fundamental characteristic of living organisms and play a crucial role in our understanding of behavior. In humans, the most widely accepted model of personality is based on five continuous dimensions, with each individual scoring differently across these factors. Recent developments in machine vision and learning algorithms have made it possible to detect and analyze a continuous range of inter-individual differences in non-human organisms. To explore this in Drosophila, we employed linear discriminant analysis (LDA) to identify new behavioral dimensions, which we refer to as identity domains. These domains reflect maximal behavioral variation between individuals while maintaining consistency within individuals over time. Using this computational framework, we investigated the complex relationships between social interaction, personality, and motivational states in flies. Our experimental paradigm involved male and female flies subjected to different social and sexual experiences for four days, after which their social group interactions were recorded. The findings offer compelling evidence of distinct inter-individual differences in Drosophila, pointing toward the presence of personality-like traits in flies. We identified four novel identity domains that differentiate between males and females and distinguish between different social and sexual experiences. In addition, we examined how the microbiome's absence affects flies' personality. Our data suggest that the lack of a microbiome leads to a significant shift in the distribution of individual flies across identity space.

Topic 23

Neuroethology

Unveiling Personality in Drosophila Melanogaster: Bridging Human Psychology with Insect Behavior

Hadar Pozeilov, Elia Dayan, Mali Levi, Oren Forkosh, Galit Shohat-Ophir
Bar - Ilan University

Individual differences, also referred to as personality, are a fundamental characteristic of living organisms and play a crucial role in our understanding of behavior. In humans, the most widely accepted model of personality is based on five continuous dimensions, with each individual scoring differently across these factors. Recent developments in machine vision and learning algorithms have made it possible to detect and analyze a continuous range of inter-individual differences in non-human organisms. To explore this in Drosophila, we employed linear discriminant analysis (LDA) to identify new behavioral dimensions, which we refer to as identity domains. These domains reflect maximal behavioral variation between individuals while maintaining consistency within individuals over time. Using this computational framework, we investigated the complex relationships between social interaction, personality, and motivational states in flies. Our experimental paradigm involved male and female flies subjected to different social and sexual experiences for four days, after which their social group interactions were recorded. The findings offer compelling evidence of distinct inter-individual differences in Drosophila, pointing toward the presence of personality-like traits in flies. We identified four novel identity domains that differentiate between males and females and distinguish between different social and sexual experiences. In addition, we examined how the microbiome's absence affects flies' personality. Our data suggest that the lack of a microbiome leads to a significant shift in the distribution of individual flies across identity space.

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View-invariant visual computations in the ancestral cortex of turtles

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Despite the importance of the cerebral cortex and its contribution to cognition, its fundamental computations remain elusive. To shed light on these computations and their evolution, we focused on an ancestral homolog of the mammalian cortex - the three-layered, thalamo-recipient, primary visual cortex of turtles. Previous experiments in anesthetized turtles indicated that while neurons in the dorsal cortex (DC) lack defined receptive fields, they exhibit spatially selective adaptation. Here we first extend these results to behaving animals. Then, by combining neurophysiology with eye cameras, we show that this spatially selective adaptation is invariant to gaze direction. Thus, DC contains information about spatial locations in allocentric coordinates. These results suggest that ancestral cortices performed computations with view invariance reminiscent of those found in the higher visual areas of mammals.

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The neural circuits governing solitary behavior in the blind mole rat

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Yeal Kashash - department of Brain Sciences, Weizmann institute
Silvia Gabriela Chuartzman - department of Brain Sciences, Weizmann institute
Yizhak Sofer - department of Brain Sciences, Weizmann institute
Noga Zilkha - department of Brain Sciences, Weizmann institute
Tali Kimchi - department of Brain Sciences, Weizmann institute

The blind mole-rat (BMR, Spalax) is a solitary, aggressive, subterranean rodent that uses seismic signals for long-distance communication, enabling it to avoid conflicts, identify competitors, and locate mates. However, the neural mechanisms underlying the BMR's solitary behavior and seismic communication remain unclear. This study aims to map the neural pathways underlying social seismic sensing and investigate the role of the oxytocinergic system in modulating solitary and social behaviors across sexes. We hypothesize that oxytocin-expressing neurons are crucial for social seismic communication and for mediating the seasonal transition from territorial aggression to mate-seeking behavior during the breeding season. We developed a custom-designed apparatus for assessing social interactions, allowing seismic and olfactory communication without direct contact, and found that socially-exposed BMRs display higher levels of communication and aggressive behaviors than controls. Preliminary whole-brain cFos mapping revealed a general increased activity in the nucleus accumbens and bed nucleus of the stria terminalis, and specifically in oxytocin-positive neurons in the paraventricular nucleus (PVN). Notably, oxytocin neuron density in the PVN was lower in BMRs than in three social mouse strains. Finally, a preliminary brain atlas of the BMR was created using MRI and CT scans, providing a valuable resource for future studies.

Topic 24

Neuroinflammation

Modulation of neuroinflammation by CBG and medical cannabis: possible implications for MS

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Multiple sclerosis (MS) is a chronic neuroinflammatory disease. Microglia play role in the pathogenesis of MS and of animal model of MS (EAE) via releasing cytokines and reactive oxygen species. The effect of specific medical cannabis and CBG on microglial inflammation and EAE is not fully understood yet. In this study, we aimed to investigate the effect of standardized medical cannabis and CBG on microglial inflammation, neurological scoring and inflammatory cells' response in EAE mice. In this study, CBG and specific standardized medical cannabis attenuated microglial production of NO, inducible nitric oxide synthase (iNOS) and TNF-α stimulated by the inflammatory inducer, lipopolysaccaride (LPS) at different concentrations. Specific cannabis strains significantly reduced the MOG-induced microgliosis, astrocytosis and infiltration of CD4 T cells in spinal cords. They also significantly decreased neuronal loss shown to be induced by MOG peptide in these sections. All MOG-treated mice developed a severe disease that peaked by day 15 post immunization. In contrast, the clinical manifestations of EAE were attenuated in mice receiving standardized medical cannabis strains or CBG upon immunization. In a therapeutic prospective, our results suggest that specific cannabis strains and also CBG may represent a therapeutic opportunity in MS, based on their multi-target properties.

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Redox and Immune dys-homeostasis interplay in Alzheimer's mice model focusing on sex differences

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Both redox and immune dys-homeostasis are involved in Alzheimer's (AD) pathology, however only a small fraction of data exists in both sexes. In our previous work we have shown that MCAT (overexpressing human mitochondrial catalase), longevity mice are more resilient to neuro-inflammation following environmental stressors and aging. We have also detected substantial sex differences in multiple behavioral and molecular outputs. We have successfully created AD model (5XFAD)/ MCAT mice to illuminate the redox – immune interplay underlaying AD. We are currently characterizing periodically sensory-motor and behavioral parameters from age 2-12 months, as well as collecting plasma samples. At the end of the study, we will perform multiple immune-histochemical and proteomic brain analyses. We also aim to investigate sex-specific differences in 5xFAD, wild-type (WT), and MCAT/5XFAD mice, to provide insights into the molecular underpinnings of AD and identify potential targets for personalized therapeutic interventions. Redox homeostasis assays will assess ROS production, catalase expression and activity, lipid peroxidation, and mitochondrial function. Neuro-immune consequences will be assessed using immunohistochemistry, flow cytometry, genomics, and proteomics. Wellbeing and cognitive outcomes will be assessed by frailty score, gait, grip strength, stress, memory and social tests. By elucidating sex-specific differences in mitochondrial redox homeostasis and immune function, this study will enhance our understanding of the molecular mechanisms underlying AD pathology and provide valuable insights into the development of sex-specific therapeutic strategies. The periodic behavioral, sensory-motor and plasma sampling will illuminate the kinetics of disease pathology as well as lead to the discovery of new multi-modal biomarkers. Preliminary data from ages 2-5 months points out the mitigation of several gait and behavioral parameters in MCAT/5XFAD compared to 5XFAD mice. The findings may lead to the identification of novel targets for intervention, paving the way for more effective and personalized treatments for Alzheimer's disease in both males and females.

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RAPID METABOLIC IMPROVEMENT INDUCED BY EARLY OBESITY REVERSAL IS ASSOCIATED WITH SUSTAINED HYPOTHALAMIC CHANGES

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Introduction: Obesity induces a low-grade inflammation affecting “metabolic organs” and the hypothalamus, where inflammation is implicated in obesity-related metabolic dysregulation. We investigated whether rapidly normalized weight loss and glycemic control correlates with hypothalamic inflammation resolution, aging effects on the ability to reverse, and possible remaining central memory to subsequent obesogenic trigger. Methods: C57BL/6 mice (7-weeks/1-year old) were fed normal chow (NC) or 60% high-fat diet (HFD) for 10-weeks. Obesity-reversal mice were switched back to NC for the last 2-weeks (‘Reverse’). After 10-weeks diet intervention, hypothalami were assessed by RT-PCR, confocal imaging, and RNA sequencing. Results: Young and mid-aged Reverse mice lost 67.91% and 58.48%, respectively, of their excess body weight, while fully restoring glycemic control following 2-weeks of obesity reversal. Nevertheless, hypothalami RNA-seq analysis revealed further aggravation of obesity-induced changes upon weight-loss, though more prominently in the mid-aged mice. Detailed immunohistochemistry analysis revealed significant hypothalamic microglial activation in HFD compared to the NC group, with only minimal reduction in the Reverse group. Conclusion: Despite rapid near-normalized glycemia and weight, only minor, if any, reversibility was documented in the hypothalamus following short-term obesity reversal. HFD-induced hypothalamic inflammation will be discussed as a mechanism underlying the complications of weight cycling with aging.

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Blood brain barrier dysfunction as a novel pathophysiological mechanism in Williams syndrome

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Objectives: Williams syndrome (WS) is a neurodevelopmental disorder caused by a heterozygous deletion of approximately 26 genes, resulting in hypersociability and distinct cognitive impairments. Among the deleted genes is general transcription factor II-i (GTF2I), a crucial regulatory gene involved in cellular transcription. While the loss of GTF2I contributes to the syndrome's unique neurocognitive features, the precise biological mechanisms remain unclear. Interestingly, similar symptoms are observed also in other neurological conditions associated with blood brain barrier (BBB) dysfunction. This phenotypic similarity prompted us to study whether there is a potential link between Gtf2i haploinsufficiency and BBB damage in WS. Specifically, we and others showed that Gtf2i deletion leads to increased inflammatory factors secretion, heightened microglial activation, nitric oxide release, mitochondrial abnormalities and abnormal intracellular calcium levels, all contribute to BBB damage.

Methods: To test if BBB impairment plays a role in the unique phenotype of WS we characterized BBB permeability and immune infiltration into the mouse brain in WS mouse model.

Result: We found altered BBB properties, along with molecular and cellular alterations suggesting that it may be beneficial to explore potential therapeutic strategies targeting BBB dysfunction.

Topic 25

New Techniques: Behavior

Naturalistic paradigm for assessing spatial memory and neuronal activity in health and disease

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Behavioral paradigms requiring many trials with a great deal of animal handling and stress, such as the Morris Water Maze and fear-conditioning paradigms, are the current golden standard in the world of behavioral research. There is a growing need for cognitive tasks fit for assessing learning and memory in a naturalistic and efficient manner, further strengthened by the novel possibility of recording simultaneous neuronal activity and underlying behavioral readings with state-of-the-art miniaturized fluorescence microscopes, or “Miniscopes”. Such a “one-shot” naturalistic task involving a complex binary maze was recently developed by the Meister group from Caltech. This assay is based on the finding that behaviors regarding ecologically relevant tasks, such as navigating burrow-like areas, are learned in the most efficient manner. Here, we modified this novel paradigm for neuronal imaging requirements and designed a flexible python-based system for maze data automation and analysis. We demonstrated this pipeline’s usability to uncover behavioral phenotypes of a model known to be particularly sensitive to stress, carriers of Apolipoprotein-ε4 (apoE4)- the most prevalent genetic risk factor for Alzheimer’s disease (AD).

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Oculomotor biofeedback for enhancing gaze control and attention measures in ADHD

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The visual system relies on complex networks involving both conscious and semi-conscious processes. Our research explores the idea that training semi-conscious eye movement processes in individuals with attention deficits can lead to adaptive changes potentially improving attention-related deficits. We designed an interactive virtual reality (VR) system that, combined with an eye tracker, provides ocular biofeedback training. Subjects maintain gaze concentration during a game that demands intensive motion. They are penalized by gradually blurring the environment and reducing background music when gaze dispersion is detected. We observed that gaze concentration improved dramatically during the biofeedback training and generalized to subsequent testing without biofeedback. This effect, quantified via the reduction in saccades and gaze dispersion in the virtual environment, was not seen in the control group, showing a significant difference. For long-term plasticity in attention-related measures, there was a notable improvement in attention indices on a widely used MOXO™ computer test for ADHD diagnostics. Our study highlights the advantages of personalized oculomotor biofeedback paradigms for individuals with ADHD, encouraging further research into enhancing their effectiveness over time and across different environments. This aims to develop ocular biofeedback-based training that can impact everyday behavior through tailored interventions.

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Binary sexually dimorphic activity in a novel cell cluster in the medial amygdala

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A growing amount of scientific attention is being paid to the issue of sexual dimorphism in the brain. Despite the many feminine/masculine parameters in brain anatomy, no clear binary properties, like in genitalia, have been demonstrated. Here, we used the TRAP2 transgenic system in mice, highlighting activity of cFos promoter, to detect neuronal populations that display sexual dimorphism. We found a dense cluster of neurons (sized 200µm) in the posterodorsal aspect of the medial amygdala (abbreviated DIMPLE) that had a full binary mode of cFos activity. DIMPLE was labeled by TRAP2 in all females but not in adult virgin males. DIMPLE, however, appeared in juvenile males before weaning as well as in adult males after sexual contact. Since the medial amygdala is known to regulate sexual behaviour, we believe that DIMPLE activity may underlie functions of either feminine behaviour or preparation to fatherhood.

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Predicting the individual's developmental Age Using Gene Expression Profiles via Machine Learning

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Genes vary in their expression levels throughout the developmental trajectory of the organism. To study the genome wide transcriptional dynamics at minutes resolution across development we have developed a new method which combines the measurements of behavioral and transcriptional states in single individuals. In particular, we first capture the behavior of C. elegans individuals across development, from egg hatching to varying time points in the L4 stage to detect the exact age of each individuals at the end of the behavioral experiment. Then, we flash freeze the worms, and extract the expression counts of over 20,000 genes across ~200 animals homogenously distributed across the L4 stage using single-individual RNAseq protocol. As a result, we can position each sample onto a developmental time trajectory and reconstruct an overall temporal view of the dynamics of gene expression across the L4 stage at minutes resolution. A fundamental question is whether one could predict the developmental age based on the gene-expression profile of the individual by machine learning. Towards this aim, I trained a convolutional neural network to predict the age of the worm within the L4 stage based on our dataset of 200 individuals in which the age and transcriptional state were defined. Overall, these results demonstrate the accurate prediction of developmental age using machine learning based on gene-expression profile of single individuals, and suggest a potential close link between the behavioral states and the underlying transcriptional modes across development.

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Topic 26

New Techniques: Data Analysis

Whole-Brain Connectivity Patterns of Local Frontal Activity: A Combined ECoG-fMRI Study

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Objectives: The Frontoparietal network is involved in executive control – cognitive processes such as attention, task-switching, and reasoning. In patients with brain tumours, surgical removal of the tumour involves functional mapping to identify critical regions and prevent post-surgery impairments. Methods: To assess regions involved in executive control locally at the vicinity of the tumour and their participation in large-scale networks, we used electrocorticography (ECoG) and resting-state fMRI (rs-fMRI). ECoG was recorded during awake brain surgery while patients completed two tasks with cognitive demand manipulation to identify brain areas associated with executive control. Change in high gamma power (70-250 Hz) with increased demand was computed using ECoG data. Functional connectivity maps based on pre-surgery rs-fMRI for each patient were constructed with ECoG electrode locations as seeds. Results: Task responsive electrodes placed on healthy-appearing and tumor-infiltrated cortex showed whole-brain connectivity patterns that overlapped with canonical rs-fMRI networks. Local task-related activity in tumour-infiltrated cortex was correlated with connectivity strength, particularly for the dorsal attention network (DAN). Tumor-DAN connectivity was associated with cognitive outcome. Conclusions: These findings demonstrate the utility of cross-modality neuroimaging for gaining insights into functional network organization in patients with brain tumors, with implications for disease treatment and rehabilitation strategies.

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Phase-amplitude coupling in executive control: Insights from ECOG during awake brain tumor surgery

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Objectives: Phase-amplitude coupling (PAC) has been implicated in executive control and other cognitive domains and is a contributor to predicting the fMRI BOLD response. Our previous findings show that high-gamma activity (70-250 Hz) may serve as a functional signature of executive control regions, as demonstrated in electrocorticography (ECOG) data in patients with brain tumors. Our aim is to investigate how phase-amplitude coupling is modulated with increased demand in executive control regions. Methods: We used ECOG data collected during task performance from the frontal cortex of 13 patients who underwent awake surgery for tumor removal. Task-related high-gamma and PAC modulations were computed for each electrode. Results: We observed high-gamma increases, with increased cognitive demand, on average 10% signal change, in 58% of the electrodes within the executive control frontoparietal network. In electrodes that showed these task-related modulations, phases of low frequency activity (e.g., in the delta and alpha range) were coupled with amplitude in the high-gamma range during task performance. Conclusions: Our findings suggest that phase-amplitude coupling may play a role in the neural mechanisms that support cognitively demanding behavior, and may serve as a good candidate measure to identify executive control regions in patients and prevent neurological damage following surgery.

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NONLINEAR DIMENSIONALITY REDUCTION OF ELECTROPHYSIOLOGICAL RECORDINGS WITH NORMALIZING FLOWS

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Despite the large number of active neurons in the cortex, for various brain regions, the activity of neural populations is expected to live on a low-dimensional manifold (Gao et al. 2017). To be able to fully learn the statistics of neural activity and to generate artificial samples, we make use of normalizing flows. We adapt the training objective of normalizing flows to improve the interpretability of the learned distribution. To this end, we transfer the concept underlying principal component analysis to the training of ANN, which helps us extract informative latent variables from those that encode less meaningful features. This helps us extract a model of the data manifold that is expressed in terms of interpretable variables of which we can estimate the dimensionality based on the most dominant latent variables. Lower-dimensional sub-spaces of that manifold that still obey the most prominent structures of the dataset can be obtained by pruning of the latent representation. Data samples within the original manifold can thereby also be mapped to its lower-dimensional counterpart, effectively implementing a de-noising mechanism. This framework is illustrated on noisy synthetic datasets and subsequently applied to electroencephalograpic recordings.

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Enhancing Latent Variable Models with Self-Consistency Regularization for Coherent Neural Dynamics

Kabir Dabholkar, *Technion Omri, Barak, Technion*

This study focuses on modeling population neural dynamics using Latent Variable Models (LVMs) based on time-series of neural spike counts. However, popularly trained LVMs tend to yield inconsistent latent trajectories between neighboring time windows. To address this limitation, we propose a self-consistency regularization approach for dynamical latents. The motivation behind self-consistency stems from its suitability for reverse engineering and its relevance to successful contrastive learning in semi-supervised tasks. By imposing self-consistency, we aim to enhance the coherence of inferred neural dynamics while encouraging low-dimensional latent representations. The results demonstrate the efficacy of self-consistency regularization in advancing LVMs, offering a promising avenue for better understanding and interpreting population neural dynamics.

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Each cell important – A Pipeline for Quantifying A-to-I RNA Editing at Single-Cell Resolution

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Adenosine-to-Inosine (A-to-I) RNA editing is the most common post-transcriptional modification and is crucial for transcriptomic diversity in the nervous system. Single-cell RNA sequencing (scRNA-seq) with the 10x platform captures data from many cells by focusing on the polyA tail. However, this approach often provides limited information per transcript, challenging its use for RNA editing analysis at the individual cell level. This limitation requires the creation of pseudo-bulk samples by combining multiple cells into one file, increasing statistical power but potentially losing each cell's individuality. To overcome this, we developed a novel pipeline that quantifies A-to-I RNA editing at single-cell resolution, leveraging the 10x platform's strengths while mitigating its limitations. We show that despite the limited per-cell data, the 10x platform does capture sufficient information in ALU elements to reliably quantify RNA editing levels across individual cells. Additionally, we observed initial signs of distinct RNA editing signatures in different cell-type populations. These findings suggest that single-cell RNA-seq, even with the limitations of the 10x platform, can be effectively used to study A-to-I RNA editing at a single individual cell level, thus elevating its importance as a way for future research into its role in neuronal function and disease.

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Topic 27

New Techniques: Electrophysiology

Stereotaxic brain surgery with neither a brain atlas nor a standard stereotaxic frame

Shaked Ron, Hadar Beeri, Or Shinover, Menachem Tur , Jonathan Brokman, Ben, Engelhard, Yoram Gutfreund, *Technion*

Acquiring experimental data in systems neuroscience often relies on stereotaxic brain surgeries for precise positioning of fine electrodes, probes and optical fibers. While stereotaxic surgery can be highly precise, its major drawback is that it can only be performed in animal species for which a brain atlas and a standard stereotaxic holding frame have been developed. Unfortunately, this includes only a hand-full of species. To overcome this obstacle we developed an alternative technique for precise brain surgery. The first stage is a surgery to glue four miniature metal markers to the skull surface. The second stage is a CT scan of the animal skull, under anesthesia. The third stage is off-line: co-registration of MRI and CT images, followed by marking the desired brain target. The final stage is the surgery for which the head is fixed in any convenient orientation. The probe, to be inserted, is attached to a positioning system and its 3D position and orientation is tracked. We used this method for positioning of Neuropixels probes in owls and quails and demonstrate its feasibility in a mouse brain. The technique enables efficient studies in non-standard animal models and provides a relatively low-cost alternative for traditional stereotaxic brain surgery.

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A bistable inhibitory OptoGPCR for multiplexed optogenetic control of neural circuits

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Information is transmitted between brain regions through the release of neurotransmitters from long-range projecting axons. Understanding how the activity of such long-range connections contributes to behavior requires efficient methods for reversibly manipulating their function. Chemogenetic and optogenetic tools, acting through endogenous G-protein coupled receptor (GPCRs) pathways, can be used to modulate synaptic transmission, but existing tools are limited in sensitivity, spatiotemporal precision, or spectral multiplexing capabilities. Here we systematically evaluated multiple bistable opsins for optogenetic applications and found that the Platynereis dumerilii ciliary opsin (PdCO) is an efficient, versatile, light-activated bistable GPCR that can suppress synaptic transmission in mammalian neurons with high temporal precision in-vivo. PdCO has superior biophysical properties that enable spectral multiplexing with other optogenetic actuators and reporters. We demonstrate that PdCO can be used to conduct reversible loss-of-function experiments in long-range projections of behaving animals, thereby enabling detailed synapse-specific functional circuit mapping.

Topic 28

New Techniques: Imaging

Voltage imaging reveals ultrafast plasticity for the error computations in the cerebellum

Sahar Zadka, Ms. Inbal Shainer, *PhD Takashi Kawashima, PhD*

Vertebrate sensorimotor behavior is mediated by a precise sequence of different neuronal activity types across the brain. Larval zebrafish is an ideal model for studying brain-wide neural dynamics, but technologies for recording neural activity at the millisecond time resolution have been limited. Here we performed population voltage imaging in three key areas for sensorimotor behaviors, including the optic tectum, cerebellum, and midbrain nucleus. The use of a light-sheet microscope with laser beam shaping and a new chemigenetic voltage indicator enabled to record from a large neuronal population stably for more than 10 minutes. We found diverse types of membrane potential modulation and spiking activity during the optomotor response. Neurons in the midbrain nucleus showed fast activation that precedes and encodes motor outputs, whereas neurons in the cerebellum and optic tectum showed delayed activation that may represent efference copy. These results provide a glimpse into the flow of sensorimotor computations in the millisecond time resolution across brain areas and demonstrate the potential for further scaling up this methodology to the whole-brain scale.

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QUANTITATIVE MONITORING OF AUTOPHAGY ACROSS NEURONAL COMPARTMENTS IN THE INTACT MOUSE BRAIN USING A NOVEL FRET/FLIM BASED BIOSENSOR

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Autophagy is a critical lysosomal degradation mechanism essential for the turnover of intracellular organelles and proteins. Proper autophagy is vital for neuronal homeostasis, and its disruption is linked to neurological disorders such as Alzheimer's, Parkinson's, amyotrophic lateral sclerosis, and autism spectrum disorder. Monitoring autophagy in neurons presents unique challenges due to its high flux, dynamic nature, and extensive compartmentalization within dendrites, axons, and cell bodies. To address this, we developed a novel pH-sensitive autophagy biosensor using Fluorescence Resonance Energy Transfer/Fluorescence Lifetime Imaging Microscopy (FRET/FLIM) for in vivo quantitative imaging in the intact mouse brain. This approach allows dynamic measurement of autophagic vacuole flux in soma, dendrites, and axons of living mice. We validated this method by using CRISPR/Cas9 to knockout Atg5, a crucial gene for autophagosome formation. This resulted in a significant reduction in autophagic vacuole density and decreased acidification. Additionally, in a cell-specific model of Tuberous Sclerosis Complex (Tsc2), associated with autism spectrum disorder and autophagy dysfunction, CRISPR/Cas9 knockout of Tsc2 increased acidification and the number of smaller, acidified autophagic vacuoles compared to control neurons. Our studies also showed that food deprivation enhances autophagy flux in individual neurons, with monitoring providing exceptional spatial and temporal resolution. This method can be used to study autophagy dynamics across various cell types, including excitatory and inhibitory neurons, astrocytes, and oligodendrocytes, and can be combined with red-shifted genetically encoded calcium sensors (xRCaMP). This innovative approach offers a way to quantitatively monitor autophagy flux with high resolution and cell specificity, advancing our understanding of autophagy in neuronal function and its role in neurodegeneration.

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FUNCTIONAL-STRUCTURAL COUPLING OF BRAIN NETWORK GRAPH THEORY IN PEDIATRIC TRAUMATIC BRAIN INJURY

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Pediatric traumatic brain injury (p-TBI) has significant and lasting effects on the developing brain, leading to changes in both structural and functional connectivity. We investigated the patterns of structural-functional circuit reorganization post p-TBI and their joint impact on cognition. Children and adolescents from all injury severities and healthy control subjects underwent structural and functional connectivity scans, clinical and cognitive evaluation in the acute and post-acute phases. Pearson correlations between graph theory measures of structural and functional connectomes were used to generate ‘coupling measures’. Our findings demonstrated differentially disrupted network topology in structural and functional brain connectomes in p-TBI compared to controls, in both acute and post-acute phases. Moreover, p-TBI patients showed lower cognitive outcomes, specifically in working memory in the acute phase, and in all executive functions in the post-acute phase. In addition, p-TBI patients displayed lower coupling measures in both phases. Finally, the coupling measures of the acute phase predicted an executive function inhibition effect in the post-acute phase. This study offers valuable insights into the complex relationship between structural and functional brain connectivity in p-TBI, highlighting the potential of multimodal coupling as a tool for understanding the impact of brain injury on connectivity and cognitive outcomes.

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Novel Bicistronic Development of Optogenetic Constructs for minimal crosstalk All-Optical Holography

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Wietek *Weizmann Institute of Science Youri, Bolsius, Weizmann Institute of Science*
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Optogenetics has revolutionized neuroscience research by allowing precise control over neuronal activity. Two-photon optogenetics allows the manipulation of single neurons, combined with activity readouts from genetically encoded sensors. In this study, we aimed to enhance the versatility of such all-optical circuit interrogation by developing soma-targeted optogenetic constructs that combine vfChrimson, a fast red-shifted channelrhodopsin, with GCaMP8, a genetically-encoded calcium indicator. By expressing these constructs with a 1:1 stoichiometry, we optimized optogenetic control and calcium imaging fidelity while reducing cell-to-cell variability. We tested six different constructs with various linkers or self-cleaving peptides in-vitro. In hippocampal cell cultures, one-photon stimulation and recording along with patch clamp demonstrated robust expression and function of the vfChrimson-GCaMP constructs with fast and high-amplitude photocurrents. Somatic restriction of both vfChrimson and GCaMP led to improved precision of stimulation and fast calcium transients with low background. The rapid decay kinetics of vfChrimson allowed low-crosstalk imaging. Our work represents a significant advancement in all-optical techniques. By combining vfChrimson and GCaMP8 to create versatile soma-targeted optogenetic constructs, we have enhanced optogenetic control and calcium imaging fidelity, paving the way for further all-optical exploration of neural circuits and their functions.

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Fluid Intelligence in Pediatric Traumatic Brain Injury: An fMRI Analysis

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Introduction: Pediatric Traumatic Brain Injury (pTBI) is a significant cause of developmental disruptions and can lead to neurocognitive impairment. While neuroimaging studies of fluid intelligence in healthy children are limited, even less is known about the neural correlates underlying this ability post-pTBI. Methods: we examined fluid intelligence in acute pTBI patients, with a particular focus on abstract reasoning abilities as a key component of this cognitive capacity. We scanned fifty-two pTBI patients with various injury severities and fifty-five healthy controls (HC) using functional Magnetic Resonance Imaging (fMRI). We examined the effect of injury severity on brain activation and identified brain regions activation during an abstract reasoning task (ARtask) post-pTBI, modeled after the advanced Raven's Progressive Matrices test. Results: Behavioral analysis revealed slowest reaction time in children with moderate-severe TBI compared to mild TBI and HC, although accuracy was not significantly affected. Reduced brain activity in the left middle frontal gyrus (MFG) among moderate-severe pTBI patients compared to HC was found. Conclusion: These results suggest that the severity of pTBI significantly impact neural processing related to fluid intelligence, and highlights the MFG as a key region involved in cognitive deficits observed post-pTBI.

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SUPER-RESOLVED INTERROGATION OF MOLECULES WITHIN THICK BRAIN TISSUES USING EXPANSION SEQUENCING

Shahar Alon, *Faculty of Engineering, Bar-Ilan University*

Molecular characterization of brain tissues using optical methods often present a problem of scale: on the one hand brain tissues are intrinsically three-dimensional (3D) structures, with thickness which can be 200 micrometers (fruit fly brain) or much larger; and on the other hand nanoscale interrogation is needed to characterize molecules within neurites and synapses, which can be ~100 nanometers in diameter. Therefore, to characterize brain tissues, an imaging technology that allows super-resolution of thick tissues is required. Another challenge is the need for multiplexed interrogation of molecules: to characterize cell types and states inside brain tissues, and to detect deficiencies in neurological conditions, one needs to measure many different molecules in their original location (i.e., in situ) within the tissue. Currently, multiplexed imaging of molecules inside brain tissues is limited to thin sections (~10 micrometers), and almost impossible with super-resolution. Here we demonstrate multiplexed super-resolved characterization of thick brain tissues, including intact human brain organoids. We perform RNA sequencing within the expanded brain tissue, and use this technology, termed Expansion Sequencing, to measure nanoscale RNA distribution within neurites and synapses, and to detect molecular deficiencies in neurological disorders by comparing disease tissues to healthy controls.

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CUSTOM-TAILORED VIRAL VECTORS FOR PROTEIN EXPRESSION IN THE QUAIL'S BRAIN

Ms. Achinoam Blau Ms., Shaden Zoabi , *Technion*

Objectives: Comparative studies across animal species are crucial in cognitive neuroscience. Research often relies on molecular tools like calcium imaging and optogenetics, which are well established in rodents but underused in non-standard models. Our goal is to enable calcium imaging of hippocampal neurons in freely behaving quails. Quails are notably resistant to many AAVs, therefore we aimed to develop custom tailored viral vectors for the quail model.

Methods: We created a protocol for culturing primary neurons from quail embryos and used these cultures to test various viruses. By analyzing the AAV receptor sequence in quails, we designed novel AAV variants.

Results: One variant, AAV1-T593K (AAV1*), showed significantly improved transduction efficiency in both in vitro and in vivo settings. Additionally, a novel strain of wildtype AAV isolated from quails (qAAAV) demonstrated better infection rates and neuron affinity in vitro. We used these custom AAVs (CAG-GCAMP6 - AAV1* and qAAAV) to transduce the hippocampal formation of quails, allowing in-vivo calcium imaging of GCAMP-expressing neurons.

Conclusions: These advancements provide a foundation for developing tailored AAVs for quails and other non-standard animal models.

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Voltage imaging in freely moving mice using Fiberscope and targeted illumination

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Recent progress in developing Genetically Encoded Voltage indicators (GEVIs) and high-speed microscopy now allows optical intracellular recordings from ensembles of neurons in awake-behaving animals. While this technology opens exciting new frontiers in neuroscience research, it is currently limited to head-restrained animals. Here we combined a multi-core optical fiber relay, a high-NA Gradient refractive index (GRIN) lens, and holographic targeted illumination using a spatial light modulator (SLM), to allow voltage imaging in freely moving mice. We validated this approach in mice expressing the GEVI Ace-mNeon2 in the CA1 region of the hippocampus. We first show that targeted illumination significantly increases the signal-to-noise ratio (SNR) and reduces photo-bleaching. Next, we demonstrate the recording of spiking and subthreshold activity at a high SNR from CA1 Pyramidal cells and interneurons during free exploration of a 2D environment at the temporal resolution of 500 Hz and a spatial resolution of ~1um. This novel experimental system paves the way for detailed mechanistic studies of neuronal dynamics during complex behavioral tasks.

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Topic 29

Plasticity mechanisms : Epigenetic mechanisms

Unraveling Intermittent Fasting's Impact on Brain Health: The Epigenetic Role of Ketone Bodies

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DNA double-strand breaks (DSBs) and reactive oxygen species (ROS) contribute to early neurodegenerative and neuropsychiatric disorders. Intermitted fasting (IF) well-established benefits for brain health prompt investigation into the underlying molecular mechanisms. During IF, the liver produces glucose and ketones, with β-hydroxybutyrate (BHB) becoming the primary brain fuel during longer fasts, as well as regulating many pathways that affect health favorably. BHB's influence on chromatin organization raises the question of whether IF's brain effects are mediated through ketone-induced epigenetic regulation. Here, mice underwent acute 24-hour fasting, with half euthanized immediately after (Fast-Ac) and the rest after additional 24 hours of food access (Refed-Ac). Additional mice experienced 15 cycles of 24-hour food access followed by fasting, with half euthanized after fasting (Fast-Ch) and half after refeeding (Refed-Ch). Fast-Ch group showed increased gene expression related to oxidative stress response (GPx1) and DNA damage repair (RAD50). Chronic IF induced chromatin conformation changes, with dynamic crosstalk between BHB, histone 3 lysine 9 tail (H3K9), and H3K27ac on promoter sites. Additionally, induced human neurons exposed to BHB displayed similar epigenetic modulation, suggesting fasting may not be necessary for these effects. In conclusion, BHB induces dynamic epigenetic changes, mediating IF's positive brain effects.

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HYPOTHALAMIC EPIGENETIC PROGRAMMING BY GREEN ILUMINATION DURING AVIAN EMBRYONIC DEVELOPMENT

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Early brain development profoundly shapes an organism's phenotype throughout life, which exhibits a remarkable sensitivity to environmental stimuli. Avian embryos, with their external embryonic development, offer a valuable model for exploring early epigenetic effects. Prolonged green monochromatic illumination (GMI) during avian incubation has been shown to significantly increase body and muscle weight, partially mediated by hypothalamic transcriptional changes. However, the precise pathway connecting light reception to the hypothalamus and the underlying mechanisms remain unclear. Here, we investigated these effects, where avian embryos were incubated in 4 lighting regimes: Dark, white illumination (WI), green illumination (GI) and green illumination only on the final three days of incubation (3GI). On the day of hatch, half of the chicks from each group were exposed to a single pulse of green illumination. Our results revealed an enhanced hypothalamic response to the green pulse only in the 3GI group. This was evident by a notable increase in the number of cFOS+ cells, indicating heightened neuronal memory. Moreover, 3GI group exhibited elevated acetylation levels on genes controlling growth, appetite, and metabolism, along with increased mRNA levels. In conclusion, embryonic GMI induces epigenetic modifications in the avian hypothalamus and promoting growth during later developmental stages.

Topic 30

Plasticity mechanisms : Glia mechanisms

THE MYELIN PROTEOME ATLAS ACROSS AGE AND SEX

Yarden Freund, *MSc student at Tal Iram's lab at the Weizmann Institute*

Myelin was once seen as a passive, permanent structure responsible for insulating and facilitating transmission of electrical signals across axons. Recent research has redefined it as an active participant in brain plasticity, highlighting its dynamic structure and ability to adapt to adult learning and experiences while also providing metabolic support to neurons. Myelin breakdown has been linked to cognitive decline and neurodegenerative diseases, with its disintegration often preceding neuronal dysfunction. Although the myelin proteome has been studied, the changes it undergoes during aging, and in a sex-dependent manner, are not fully understood. In this project, we have isolated myelin proteins from young (3 months), middle-aged (13-16 months) and aged (27-29 months) male and female mice. Through integration of unbiased proteomics with advanced analytical techniques, we aim to establish an in-depth characterization of the myelin proteome. Using mass spectrometry-based proteomics, we identified 3,475 unique proteins in myelin with 889 significantly altered with age. By comparing our findings with published RNA-seq datasets, we seek to uncover potential protein targets and pathways involved in myelin degradation and age-related cognitive decline. Overall, we present a comprehensive myelin proteome atlas that offers valuable insights into the molecular mechanisms affecting myelin integrity and function with aging.

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Topic 31

Plasticity mechanisms : Neuronal excitability

NMDA RECEPTORS MAINTAIN HOMEOSTATIC FIRING RATE SET POINTS IN HIPPOCAMPAL CIRCUITS

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What molecular mechanisms do neurons use to homeostatically maintain their activity at a given set point? While NMDA receptors (NMDARs) are the classic, central regulators of Hebbian-like synaptic plasticity, their role in homeostatic plasticity has remained controversial. Methods: To measure network activity: Long-term multi-electrode array recording in primary hippocampal neurons, and tetrodes for single unit activity and local field potentials (LFP) from CA1 stratum pyramidale in vivo. Patch clamp whole-cell recordings to assess changes in cellular and synaptic properties. Results: Utilizing long-term multi-electrode array recordings in hippocampal networks ex vivo, we found that sustained inhibition of NMDARs by structurally different blockers, including ketamine, rapidly and stably suppressed mean firing rate (MFR), while maintaining homeostatic responses to activity perturbations. Interestingly, ketamine reduced MFR set point through an intrinsic, but not synaptic, mechanism that ultimately lowers the excitation/inhibition (E/I) ratio. This mechanism requires eEF2K and BDNF. Importantly, chronic local delivery of NMDAR blockers to the CA1 suppressed MFR set point across vigilance states in behaving mice. Altogether, our results indicate that the degree of NMDAR activation dictates homeostatic MFR set point. These results highlight NMDARs as a network-wide MFR set-point modulator and extend NMDAR function beyond its canonical role in synaptic plasticity.

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Design of Ultrapotent Genetically Encoded inhibitors of Kv4.2 for Gating Neural Plasticity

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The Kv4.2 potassium channel plays established roles in neuronal excitability, and in plasticity. Current means to study the roles of Kv4.2 are limited, motivating us to design a genetically-encoded membrane tethered Heteropodatoxin-2 (MetaPoda). We find that MetaPoda is an ultrapotent and selective gating-modifier of Kv4.2. We narrow its site of contact with the channel to two adjacent residues within the voltage sensitive domain (VSD) and, with docking simulations, suggest that the toxin binds the VSD from within the membrane. In neurons, we show that MetaPoda specifically, and potently, inhibits all Kv4-currents, leaving all other A-type currents unaffected. Inhibition of Kv4 in hippocampal neurons does not promote excessive excitability, as is expected from a simple potassium channel blocker, however prolonged expression increased the immediate early gene cFOS. We go on to discover that the functional outcome of prolonged Kv4.2 inhibition with MetaPoda is prevention of short-term potentiation (STP). These findings argue for a major role of Kv4.2 in facilitating plasticity of hippocampal neurons. Lastly, we find that our engineering strategy is suitable for the swift engineering of another potent Kv4.2-selective membrane-tethered toxin, Phrixotoxin-1, denoted MetaPhix. Together, we provide two uniquely potent genetic tools to study Kv4.2 in neuronal excitability and plasticity.

Topic 32

Plasticity mechanisms : Pre-post synaptic mechanisms

Plasticity stability and rhythmogenesis via STDP

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Oscillatory brain activity has intrigued neuroscientists for nearly a century, with various frequency bands linked to specific neural or mental states across animal species. Theoretical models have successfully induced rhythmic activity by artificially tuning synaptic connections. However, the mechanism controlling this tuning for oscillatory behavior remains a fundamental question. It is well-known that unsupervised learning through synaptic plasticity plays a pivotal role in achieving oscillatory behavior. Particularly, Spike-Timing-Dependent Plasticity (STDP), a prominent learning rule, modifies synaptic strengths based on the timing of pre- and post-synaptic spikes. Here, we employ a rate model with excitatory and inhibitory neurons to explore the impact of asymmetric pair-wise STDP rules on synaptic weights. Our findings demonstrate that these learning rules induce critical rhythmogenesis, and prevent the network from dividing into clusters.

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L1 NDNF INTERNEURONS CONTROL EXPERIENCE-DEPENDENT PLASTICITY IN ADULT CORTICAL CIRCUITS

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Experience-dependent plasticity is essential for an animal's ability to adapt to and learn from the environment. Though inhibition has been shown to be important in this process, the molecular, cellular and circuit mechanisms underlying this process are poorly understood. NDNF interneurons in cortical layer1 receive long-range sensory and contextual input and target the apical dendrites of lower-layer pyramidal neurons. Thus, since synaptic plasticity of apical dendrites is thought to control cortical circuit plasticity, we hypothesize that L1 NDNF INs are in prime position to govern this process. Focusing on the adult visual cortex, we perform monocular deprivation (MD) followed by acute slice electrophysiology, revealing that excitatory inputs onto L1 NDNF INs are strengthened following MD. Then, using longitudinal 2p imaging we find that L1 NDNF INs are plastic following MD. We next inhibit L1 NDNF IN activity, which leads to a loss of ocular dominance plasticity (ODP) in L2/3 pyramidal neurons of the visual cortex. Finally, using a novel approach for RNA-Seq in very small populations, we find a group of genes whose expression patterns change in NDNF INs following MD. Taken together, these experiments indicate a key role for L1 NDNF INs in regulating the plasticity of cortical circuits.

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Acute mAID2-mediated degradation of synaptic molecules as a tool for studying synaptic biology

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Evaluating the roles of proteins of interest (POI) through genetic approaches (gene knockout, RNA interference) is limited by the procedure's irreversibility and slow POI loss kinetics, challenging the ability to assess acute and temporary effects of POI elimination. These limitations also apply to synaptic POIs. Here we describe the use of Auxin-Inducible Degron 2 (AID2) technology to determine the effects of rapid and reversible elimination of the key synaptic scaffold proteins PSD-95, GKAP and Gephyrin on synaptic properties. To that end, we expressed fusion proteins of each of these POIs with fluorescent reporters and the mAID degron together with the OsTIR1 E3 ubiquitin ligase in rat cortical neurons in culture. Exposure to the auxin derivative 5-ph-IAA was followed by rapid loss of each POI, followed by slow recovery upon 5-ph-IAA removal. Elimination was effective for both XFP and HaloTag fusion proteins, and for C-terminal, N-terminal, or internal degron fusion loci. As expected, PSD-95 and Gephyrin elimination reduced AMPA and GABA receptor contents, respectively. Surprisingly, however, elimination of GKAP but not PSD-95 seemed to significantly reduce synaptic 'size'. These findings illustrate the utility of the AID2 system for studying the roles of synaptic POIs and possibly those of many others.

Topic 33

Psychiatric and neurodevelopmental disorders : Anxiety

The Neuronal Function of Neurensin-2

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Neurensin-2 is a vesicular-membrane protein with a selective and dynamic expression in hippocampal inhibitory neurons. Neurensin-2 expression peaks in limbic regions after chronic stress and is attenuated following treatment with antidepressants. These dynamic expression levels directly regulate anxiety and depression-like behaviors in mice, as well as the effect of chronic treatment with antidepressants. The cellular role of Neurensin-2 and how this cell-type-specific protein alters neuronal function are poorly understood. We showed that Neurensin-2 dramatically enhances AMPA-receptor-mediated currents However, the molecular mechanisms underlying this effect are still unknown. In the current study, we aimed to elucidate the cellular role of Neurensin-2 in neurons. First, we colocalized Neurensin-2 with different cellular vesicle markers to identify what vesicle subtypes Neurensin-2 is incorporated into. Then, we aimed to apply molecular approaches to elucidate the effect of Neurensin-2 induction on the intracellular distribution of AMPA receptors. The results of this study shed light on the neuronal function of a newly-discovered depression-mediating protein with significant therapeutic potential. Further characterization of Neurensin-2 will elucidate how this protein mediates depression and provide novel intervention strategies to treat this devastating disorder.

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Exploring brain-wide neural dynamics underlying psilocybin's psychoactive and anxiolytic effects in zebrafish

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Traditional anti-anxiety and antidepressant medications, such as serotonergic drugs, are limited in their efficacy in many patients. Serotonergic psychedelics are promising emerging therapeutics for such psychiatric disorders, yet their underlying mechanisms of action in the brain remain largely elusive. Zebrafish have evolutionarily conserved serotonergic circuits, including subcortical targets such as the habenular and brainstem regions, making it a promising model for studying subcortical pathways of serotonergic drugs. Psilocybin, a psychedelic serotonin receptor agonist, was shown to have stress-mitigating effects on zebrafish behavior. Here, we investigated the brain mechanisms of the anxiolytic effects of psilocybin on larval zebrafish brain-wide neural dynamics during stress. Using whole brain light-sheet imaging during a stress paradigm, we uncovered several brain regions responding to psilocybin treatment. The habenular complex, linked to the stress response in mammals, was inhibited during stress in fish under psilocybin treatment, compared to increased activity in control fish. These findings provide direct insights into how serotonergic psychedelics impact subcortical networks to affect animal behaviors.

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The function of the Claustrum in response to psychedelic drugs

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Depression affects approximately 5% of the global population, presenting significant personal and societal challenges. In some cases, traditional antidepressants have limited efficacy and severe side effects. Ketamine is a rapid-acting antidepressant, that has shown a 50% success rate in treating treatment-resistant depression, although it requires repeated dosing. Psilocybin, naturally occurring psychedelic compound, may offer long-lasting therapeutic benefits by a single dose, primarily targeting the 5-HT2AR and showing sustained improvements in depressive symptoms. The claustrum, a highly interconnected brain region enriched with 5-HT2AR and KOR, is implicated in modulating depressive behaviors and may mediate the therapeutic effects of psychedelic drugs. Our work aims to explore the role of the claustrum in mediating anti-depressant effects of psychedelics. We'll use depression-like model in mice, induced by chronic corticosterone consumption in drinking water. Afterwards, we'll conduct behavioral tests to assess locomotor activity, anxiety, and depression-like behaviors. By local infusion of 5-HT2AR or KOR agonists to the claustrum, we will verify the claustrum's involvement in antidepressant effects of the psychedelic drugs. Additionally, we will employ chemogenetic techniques (DREADDs) to modulate claustrum neuronal activity during the behavioral tests. This approaches will provide insights into the function of the claustrum in mediating antidepressant effects of psychedelic drugs.

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Investigating the neural circuits involved in OCD-associated behavioral dysfunction

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Obsessive-compulsive disorder (OCD) is a prevalent and debilitating neuropsychiatric condition marked by intrusive thoughts (obsessions), repetitive behaviors (compulsions) and usually accompanied by anxiety. Conventional treatments like SSRIs, which are also the first-line therapy for anxiety and depression, often fall short, with around 40% of patients not responding1–3. This underscores the need for a better understanding of the disorder's underlying mechanisms, as the connection between anxiety and compulsivity and the specific dysfunctions in circuitry and physiology remain unclear4–6. This study aims to investigate the neuronal mechanisms and circuits underlying the emergence and consolidation of OCD-related compulsive behaviors, with a particular emphasis on the role of anxiety in governing these compulsive actions. We focus on the Sapap3-KO mice model of OCD, which exhibits high anxiety levels and compulsive self-grooming behavior8. To study stress-induced grooming in mice, we developed a novel stress-inducing behavioral paradigm that allows high-resolution behavioral tracking, combined with neural recording and manipulation experiments. Using this system, we show altered stress-induced grooming in SAPAP3-KO mice compared to WT littermates. Through multi-region c-Fos analysis, we identified specific brain regions that exhibit increased activity during the stress-inducing phase of the paradigm, which we are currently investigating with targeted fiber photometry recordings. Additionally, we characterized a novel “KO-phenotype severity index,” which indicates the severity of phenotypic abnormalities and correlates with the intensity of compulsive self-grooming. Our findings provide new insight into the links between stress and compulsive grooming behaviors in the context of OCD.

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A whole-brain screen reveals the pivotal role of the perirhinal cortex in social avoidance and anxiety behavior

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Social interactions involve complex strategies, including approaching beneficial and avoiding threatening conspecifics, which are key to understanding social anxiety. This study investigates stimulus-specific social approach and avoidance using a novel social avoidance learning paradigm. While brain regions involved in classical anxiety and fear are known, those linked to social fear and anxiety remain elusive. We conducted an unbiased whole-brain screening of immediate early genes (c-Fos and Arc) to label active cells basis of social valence following social fear training. Our results highlight both established regions, like the basolateral amygdala and prefrontal cortex, and novel areas, including the perirhinal cortex (PRC), CA2, claustrum, and nucleus accumbens, in social fear-related behaviors. The PRC, previously linked to spatial memory, also plays a role in responding to aversive social stimuli. Using fiber photometry recordings and optogenetics and chemogenetic manipulations, from PRC, we explored its role on social preference and social fear memory recall. Additionally, we used AAV and rabies viral tracing to map the targets in the PRC circuit. These findings would enhance our understanding of the neural mechanisms behind social avoidance, offering potential therapeutic targets for social anxiety.

Topic 34

Psychiatric and neurodevelopmental disorders : Autism

Perturb-seq reveals divergent and convergent pathways in autism associated genes through early cortical differentiation

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Autism Spectrum Disorder (ASD) is a group of symptomatically heterogeneous neurodevelopmental disorders. ASD is known to have a strong genetic basis; however, its genetic architecture is very complex. The heterogeneity of the symptoms may stem, at least partially, from genetic heterogeneity. In this study, we employ a combined approach of CRISPR screening and single-cell RNA sequencing (Perturb-seq) to examine the effects of mutations in 39 high confidence ASD-associated transcription regulators on early in-vitro cortical differentiation of human embryonic stem cells. Our findings reveal that mutants tend to exhibit premature differentiation towards either neuronal cells or oligodendrocyte (OD)-like cells, correlating with known human phenotypes of the same genes. For example, perturbations that increase OD-like cells are more likely to be associated with microcephaly, while perturbations that decrease OD-like cells and increase neuronal cells are more likely to be associated with macrocephaly. Additionally, integrating cell-type composition changes with gene expression data enhances the distinction between genes predominantly associated with ASD and those predominantly associated with developmental delay. Our results advance the understanding of the genotype-phenotype relationship in ASD, potentially aiding in the identification of genetic subgroups within ASD and the development of targeted treatments.

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Characterization of the thioredoxin antioxidant system in autism spectrum disorder

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Objectives: Increased oxidative stress was found in the brain of autism spectrum disorder (ASD) patients, which may impair brain development. Thioredoxin (Trx) system is one of the most important endogenous antioxidant systems. Here, we investigated the link between ASD and the abnormalities in cellular antioxidants, focusing on the Trx system. Methods: The cortices of the wild-type (WT) and Shank3 KO mice (a model of ASD) were extracted and used for Western blot analysis of thioredoxin 1 (Trx1), thioredoxin 2 (Trx2), and thioredoxin reductase 1 (TrxR1). Additionally, TrxR1 levels were evaluated in the cortex sections by immunohistochemistry. To prove the link between the Shank3 gene and the Trx system, Trx1 levels were assessed by Western blots in the SH-SY5Y cells with or without the Shank3 gene deletion. Results: A significant downregulation of several studied components of the Trx system was observed in Shank3 KO compared to the WT mice. The Shank3 gene deletion also significantly reduced the levels of Trx1 in SH-SY5Y cells. Conclusions: Our observations suggest that ASD pathogenesis may be associated with the lack of cellular antioxidant defense, in particular Trx system. These findings give additional insight into the mechanisms underlying the ASD pathology.

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Involvement of amygdala neurons in male predominance of autism spectrum disorder

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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 arc-dVenus-labeled cells of Pogz+/- mice. Are current result present three different type of principal neurons in the BLA varied in active properties of the cells. We aim to identify the distribution of those neurons among the groups possibly indicate sex differences among the active neurons in Pogz+/- and control mice.

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The sex differences in the synaptic phenotype of the autistic mouse models

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Haitham Amal, *Institute for Drug Research, School of Pharmacy, Faculty of Medicine, The Hebrew University of Jerusalem, Jerusalem, Israel*

Objectives: Synaptic abnormalities are essential contributors to autism spectrum disorder (ASD). The prevalence rate of male individuals diagnosed with ASD prevails over females in a proportion of 4:1. Therefore, males remain the main focus in ASD studies. But should we pay attention to ASD in females as well? Here, we studied the sex differences in the synaptic phenotype of two ASD mouse models, Shank3Δ4-22 and Cntnap2-/- mutant mice of both sexes. Their wild-type littermates were used as controls. Methods: The mouse cortices and striata were extracted and used for the evaluation of the synaptic phenotype. Levels of glutamic acid decarboxylase 67 (GAD1), N-methyl-D-aspartate receptor subunit 1 (NR1), vesicular glutamate transporter (VGAT), and synaptophysin (Syp) were measured by Western blots. The dendritic spine density (SD) was assessed using confocal microscopy. The social behavior of mice was assessed using the three-chamber sociability test. Results: SD and the GAD1, NR1, VGAT, and Syp levels were significantly reduced in both ASD models compared to the control indicating impaired synaptic development in the mutant mice. However, no sex differences in these parameters were found. Conclusion: Thus, female ASD mice develop similar synaptic abnormalities as males and need to be studied along with the male animals.

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Gsk3β: A promising therapeutic target in the Cntnap2 -/- mouse model of autism

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Background: Core behavioral deficits of autism spectrum disorder (ASD) have been reported in humans with CNTNAP2 mutation. The Cntnap2 knockout mice (Cntnap2-/-) exhibit essential ASD-like behavioral phenotypes. Objectives: In this study,we aimed to test the hypothesis that a mutation in the Cntnap2 gene leads to a reprogramming in the protein expression and kinase signaling which could potentially lead to synaptic and behavioral dysfunction. Methodology and principal findings: We tested our hypothesis by conducting global- and phospho-proteomicsbased mass spectrometry followed by biochemical studies. The phosphoproteomics analysis revealed a significant reduction in the phosphorylation levels of Glycogen Synthase Kinase 3 beta (Gsk3β) at serine 9 in the mutant mice, suggesting an aberrant over-activation of Gsk3β in their cortex. Moreover, Gsk3β phosphorylated β-catenin and resulted in its ubiquitination and degradation, and thus a downregulation of WNT/β-catenin signaling pathway.Treatment with a selective inhibitor of Gsk3β, HU-56, improvedsociability deficits and anxiety in these mice. These effects were accompanied by increased levels of GAD1, a marker of GABAergic neurotransmission. Conclusions:Gsk3β appears to be a critical contributor to the cellular and behavioral deficits in Cntnap2-/- mice. Therefore, our findings suggest that targeting Gsk3β could be a promising therapeutic approach for treating ASD-like phenotypes associated with CNTNAP2 mutation.

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UNDERSTANDING THE METABOLIC ALTERATIONS INVOLVED IN THE EARLY DEVELOPMENT OF ANGELMAN SYNDROME

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Angelman Syndrome (AS) is a rare neurodevelopmental genetic disorder caused by the loss of function of the UBE3A gene, affecting approximately 1:15,000 live births. We have recently shown that mitochondrial functioning in AS is altered during mid to late embryonic brain development leading to increased oxidative stress and enhanced apoptosis of neural precursor cells. However, the overall alterations of metabolic processes are still unknown. Hence, we aim to investigate the metabolic profiles of wild-type and AS littermates and to identify which metabolic processes are aberrant in the brain of AS model mice during embryonic development. We collected brain tissue samples from mice embryos at E16.5 and performed metabolomic analyses using proton nuclear magnetic resonance (1H-NMR). Multivariate and Univariate analyses were performed to determine the significantly altered metabolites in AS mice. Our study revealed distinct alterations of specific metabolites, related to energy metabolism (Pyruvate metabolism and Glycolysis/Gluconeogenesis), and mitochondrial respiration (Citric acid Cycle), providing valuable insights into the metabolic consequences of UBE3A loss of function in early neuronal development. To conclude, UBE3A loss of function alters bioenergy-related metabolism during embryonic development. This insight can serve later for the development of novel therapeutic strategies.

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ATP synthase c-subunit upregulation causes mitochondrial dysfunction in Shank3 mouse model of autism

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Objectives: A strong link between the SHANK3 gene mutations and autism spectrum disorder (ASD) has been established but its molecular mechanisms remain unknown. Our preliminary proteomics study revealed an aberrant protein expression of ATP synthase c-subunit in the brain of the Shank3Δex4-22 mice. This aberrant expression affects ATP-synthase activity and may lead to mitochondrial dysfunction.Consequently, we aimed to investigate the role of this subunit and mitochondrial dysfunction in the Shank3 mice. Methods: Global proteomics of the cortex in Shank3Δex4-22 and its wild-type (WT) mice were further analyzed. Mitochondrial membrane potential (MMP) and proton leak were assessed in the cortical neurons isolated from both groups. Shank3Δex4-22 was treated with HU-55, which modulates the ATP synthase leak, and the behavior of these mice was investigated. Results: The c-Subunit protein level was significantly increased in the cortex of Shank3Δex4-22 mice. Additionally, the cortical neurons of these mice exhibited increased mitochondrial proton leak and a reduction of MMP, indicating mitochondrial dysfunction.Treating the mutant mice with HU-55 attenuated autistic-like behavior. Conclusions: Mitochondrial dysfunction appears to be implicated in the Shank3 mutant mice,possibly due to the aberrant protein level of the c-subunit.These findings provide a new potential direction in the search for therapeutic interventions for ASD.

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Characterization of brain immediate-early genes expression in mice exposed to various emotionally aroused conspecifics

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Social cognition involves the perceiving and interpreting of social cues exchanged between individuals, which are imperative for the adaptive response of a subject to the social milieu. Emotion recognition, corresponding to the ability to discern the emotional states of others, plays a pivotal role in various pro-social behaviors, such as emotion contagion, empathy, and helping behavior. This capacity, which allows an individual to adapt its behavior to the emotional states of others, is known to be compromised in individuals diagnosed with autism spectrum disorder (ASD). While previous research has identified several brain regions involved in emotion recognition, a comprehensive understanding of the whole-brain neural networks underlying emotion cognition at the cellular level remains elusive. We aimed to investigate the neural correlates of emotion recognition in mice by quantifying whole-brain neuronal activation patterns in response to emotionally diverse social stimuli. The differences in neuronal activity across various brain regions were assessed by changes in immediate-early gene (IEG) expression (Arc and c-Fos), which can be quantified by genetic and immuno-histological techniques. We mapped neuronal activation of male Arc::dVenus mice, in response to encounters with stressed, isolated and neutral male, as well as female conspecifics. High-resolution microscopy and Neuroinfo software were used to systematically visualize and quantify the expression of Arc and C-Fos across the brain, enabling the creation of detailed 3D brain maps and precise quantification of neuronal activation. Using bioinformatic tools, we created a correlation matrix of different brain regions and compared them across different conditions. Ultimately, these findings will contribute to a deeper understanding of the neurobiological basis of social behavior, with potential implications for the diagnosis and treatment of neurodevelopmental disorders characterised by social deficits, such as ASD.

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Increasing feedback salience may improve performance monitoring in autism

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Objectives Performance monitoring, essential for smooth cognitive, affective, and motor processes, is impaired in autism spectrum disorder (ASD). We aimed at analyzing one of the key EEG indices of performance monitoring, the Feedback-related negativity (FRN), in a perceptual discrimination task. FRN is known to be largely generated by the Anterior cingulate cortex (ACC) that plays a crucial role in performance monitoring. Methods EEG at Cz was recorded in 25 ASD and 23 neurotypical (NT) participants during a two-tone discrimination task in Original and Modified protocols, the latter providing feedback with increased visual salience. FRN was calculated as a difference between evoked neuronal responses to Correct vs Incorrect trials. Results While accuracy was comparable in both groups, ASD showed much higher accuracy variability, accounting for the lowest (around 50%) and highest (100%) scores. Despite comparable accuracy to NT, ASD showed significantly smaller FRN ($p=0.016$), replicating Zuk et al., 2024. However, when feedback salience was increased group difference was no longer significant ($p= 0.725$), suggesting the increasing visual salience may facilitate performance monitoring in ASD. Only in ASD group, good performers showed significantly larger Post-error slowing (PES), characterized by slower responses following incorrect versus correct trials. Two thirds of ASD increased PES in Modified protocol compared to Original protocol. Those ASD who slowed their responses after mistakes when feedback was more salient, showed on average 10% decrease of the response time. Conclusions The diminished FRN in ASD compared to NT may indicate reduced sensitivity to external feedback. The reduction of intergroup differences in the Modified protocol as well as acquired behavioral cautiousness (slowing responses after errors) suggests that enhancing the external characteristics of feedback may to some degree alleviate performance monitoring difficulties in ASD.

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Cytoskeletal changes in SHANK3 mutation mouse model cortex

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The study aimed to investigate the neurobiological mechanisms underlying Autism Spectrum Disorder (ASD), focusing on the SHANK3 mutation, a significant genetic risk factor for ASD affecting around 1%-2% of people on the spectrum. Furthermore, SHANK3 deletion has been implicated in Phelan-McDermid syndrome, which is highly debilitating. Using a mouse model with a human-like SHANK3 mutation (InsG3680), we examined deficits in both neurons & oligodendrocytes, overall brain development, physiology, and behavior. To explore the cellular and molecular consequences of this mutation, we conducted both in-vivo and in-vitro studies, focusing on cytoskeletal elements, particularly actin stabilization. The SHANK3 mutant mouse model displayed neurobiological alterations , with notably in properties related to actin stabilization, affecting the cellular skeleton. These deficits were characterized across different developmental stages in brain regions associated with autistic features. The findings suggest that SHANK3 mutations contribute to the developmental and physiological abnormalities observed in ASD, providing insights into critical periods of brain development associated with autistic traits.

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Pharmacological Targeting to Restore Oligodendrocyte Function in a SHANK3 Autism Mouse Model

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Objectives: autism spectrum disorders (ASD) have a strong genetic component, with mutations in the SHANK3 gene accounting for 1% of all ASD cases. Shank3 is a scaffold protein vital for synaptic development and function, extensively studied for its role in neuronal synapses, particularly in linking glutamate receptors to the cytoskeleton. However, we recently found an essential role for Shank3 in oligodendrocyte-neuronal synapses. Here, we investigated the potential of targeted pharmacological interventions to restore impaired glutamate-mediated communication in oligodendrocyte-neuronal synapses resulting from the InsG3680 mutation in Shank3. Additionally, we studied whether such interventions ameliorate myelination deficits and rescue the autistic phenotype in the InsG3680 mouse model, with an emphasis on evaluating the translational relevance of these findings for potential human treatments.

Methods: we employed molecular, imaging, and behavioral methods both in vitro and in vivo to evaluate changes in myelination and oligodendrocyte-neuronal synaptic function.

Results: our results indicate that the targeted pharmacological manipulation improves calcium signaling in vitro, suggesting enhanced communication at the oligodendrocyte-neuronal synapse. This was associated with alterations in behavioral tests and molecular properties, suggesting potential positive outcomes on myelination and synaptic function in the InsG3680 mouse model.

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Minimally verbal children with autism "see the point, but do not point it out": A behavioral and eye-tracking study in visual perceptual processing

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Yoram Bonneh, *School of optometry and vision sciences and Gonda Multidisciplinary Brain Research Center, Bar Ilan University*

Objectives: During the first year in typical development, basic visual object recognition emerges. Little is known about visual perceptual processing of the minimally verbal with autism (mvASD). Methods: Twenty mvASD children completed visual processing tasks: pointing to odd target among distractors, detecting contour among Gabor elements, and viewing a Kanizsa triangle with modulated versions. Eye gaze and pointing distance from oddball and Kanizsa center were recorded. During "Kanizsa dragging game," participants matched shapes to Kanizsa. Results: Two groups emerged in low-level vision tests: eleven participants detected the oddball at ceiling, while 9 performed near chance. Strikingly, low performers' eye gaze exceeded chance and outperformed pointing. Performance improved with less distractor saliency but declined with increased complexity for some high performers. In Kanizsa task, gaze and pointing shifted to center in modulated versions, and high performers successfully matched shape to Kanizsa. Conclusions: Performance was sensitive to distractor saliency and stimulus complexity, suggesting early visual processing differences and visual perception based on low-level representations with attenuated inference-based processing. However, eye-gaze superior to pointing, shifting of pointing and gaze towards center and successful Kanizsa shape-matching, indicate performance doesn't solely rely on what they perceive, but also ability use visual signal to drive behavior.

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Metabolic and Mitochondrial Dysregulation in Angelman Syndrome: Linking Oxidative Stress to Embryonic Neural Development.

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Angelman syndrome (AS) is a rare neurodevelopmental disorder caused by the loss of UBE3A gene function and is linked to elevated levels of reactive oxygen species (ROS). However, the origin of this oxidative stress during AS embryonic development is poorly understood. Here, we identify significant mitochondrial disruptions in AS embryonic brain neural cells, including heightened mitochondrial membrane potential, depleted glutathione levels, and increased mitochondrial ROS, leading to enhanced apoptosis. Metabolomic profiling further reveals specific metabolic alterations in AS embryonic brain tissue, including elevated acetate, lactate, and succinate levels associated with pyruvate and glycolytic pathways, indicating impaired bioenergetic metabolism. Together, these mitochondrial and metabolic dysfunctions suggest that bioenergetic disruption in AS contributes to ROS accumulation and oxidative stress during critical stages of neural development. Our findings provide key insights into the role of mitochondrial and metabolic dysfunctions in AS pathogenesis and highlight oxidative stress as a potential shared mechanism across neurodevelopmental disorders. Unveiling the link between oxidative stress, mitochondrial function, and neuronal development offers a promising avenue for therapeutic intervention in AS, with implications for related disorders marked by similar oxidative and metabolic disturbances.

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The role of nitric oxide-mediated glutamatergic alterations in the Shank3Δ4-22 mouse model of autism

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SHANK3 gene is mutated in 1% of ASD cases. SHANK3 codes for a major scaffolding protein in glutamatergic neurons having central role in post-synaptic density structure. Shank3Δ4-22 mouse model exhibits the behavioral phenotype of ASD and is used here. Previously we showed that nitric oxide (NO) signaling is impaired in ASD mouse models, however the exact mechanism causing excessive NO is unknown. We hypothesize that SHANK3 deficiency causes imbalance in maturation of glutamatergic synapses which could potentially lead to the ASD-related behavioral deficits. We discovered dysregulation of the glutamatergic receptors expression in brains of KO mice, which defines the nature and activity of synapses. Using selective nNOS inhibitor, reversed glutamatergic alterations in the KO mice. To understand how exactly NO affects different proteins we focused on PSD-95 protein, We showed that in the KO mice, there is over-ubiquitination of PSD-95, reversed by nNOS inhibition- suggesting that NO causes poly-ubiquitination and degradation of PSD-95. Using SH-SY5Y cells with SHANK3 deficiency, we showed that a selective antagonist to NMDAR2B subunit reduces nNOS activity and NO production. In conclusion, we deciphered a novel crosstalk mechanism between NO and the glutamatergic system, which may lead to the discovery of novel drug targets for ASD.

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Topic 35

Psychiatric and neurodevelopmental disorders : Drugs of Abuse and Addiction

"A SOBERING FRIENDSHIP" – THE EFFECTS OF DAILY SOCIAL & PROSOCIAL BEHAVIOR ON RELAPSE TO ALCOHOL

Hila Flumin, Segev, Barak, Inbal, Bartal Ben-Ami,

Tel Aviv University

In recent years, research demonstrated the powerful impact potential social environment has on substance use in addiction and abuse. Studies have seen effects of social contact on drug abuse in rodent models, yet such effect hasn't been observed for alcohol addiction models. We aimed to test the idea that a different type of social interaction, prosocial, could demonstrate an effect. Prosocial behavior is associated with reward circuits like the Nucleus Accumbens, thus potentially making a stronger neural and behavioral overlap with addiction than simple social contact. Here we present a novel paradigm based on a combination of well-validated alcohol-drinking models (2 Bottle Choice & Operant Self-administration of Alcohol) and a rat helping behavior test (HBT) where rats are able to engage in a daily act of helping by releasing a trapped cagemate. that is aimed at testing potential effects of social and prosocial behavior on addiction. In this experiment, relapse tendency was tested in alcohol-abstinent rats in "helping" or "no-helping" conditions. Next, biological mechanisms mediating the effects of prosocial behavior on alcohol addiction and relapse will be examined. The results of this research may provide insight on the neural circuits underlying addiction and help developing novel strategies to reduce relapse.

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The Effect of MDMA on Alcohol Memory Reconsolidation and Relapse

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Objective: Alcohol use disorder is a relapsing condition with ~70% of individuals relapsing within a year, necessitating relapse-preventive treatments. Environmental cues associated with alcohol reinforcement often trigger relapse; thus, targeting cue-alcohol memories could suppress relapse. Memories become temporarily changeable upon retrieval during memory reconsolidation. Here, we tested whether 3,4-methylenedioxymethamphetamine (MDMA), known to enhance memory flexibility, can attenuate relapse to alcohol when administered during the reconsolidation of alcohol-related memories in a long-term alcohol self-administration model. Method: Rats were trained to voluntarily consume alcohol in the intermittent access two-bottle choice procedure for 8 weeks. Following 10 days of abstinence, rats were injected with MDMA (5, 10 mg/kg; i.p.) or vehicle. Relapse was tested at three time points after the treatment. Results: When tested one day after memory retrieval+treatment, vehicle-treated rats showed considerably higher relapse to alcohol drinking compared with the MDMA-treated rats. However, this effect diminished in the long term. Conclusion: MDMA attenuates relapse to alcohol in the short term and suppresses the degree of relapse overall. These results point to the potential of MDMA to repress pathogenic drug memories using reconsolidation mechanisms as prevention treatments.

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IDENTIFYING PERIPHERAL BIOMARKERS FOR OPIOID USE DISORDER – A MOUSE MODEL

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Objectives: Opioid use disorder (OUD) is a significant health, societal and economic problem worldwide. Currently, there are no reliable physiological biomarkers for addiction. Diagnosis and treatment progress is mainly determined by subjective clinical assessment. Therefore, it is crucial to identify and characterize a set of biomarkers for substance addiction.

Methods: We used addiction-related animal models, namely, opioid-induced behavioral sensitization, and voluntary opioid self-administration. We collected blood samples at several time points during training. Finally, we examined how proteins in the serum correlated with behavioral sensitization and drug consumption and used multiple linear regression (MLR) to predict sensitization and consumption based on these proteins.

Results: As expected, opioid-treated mice exhibited dose-dependent locomotor sensitization. We found that certain blood proteins correlated with the escalation of opioid-related behaviors. Moreover, we found that the combination of several proteins predicted opioid-induced sensitization more accurately than individual proteins, accounting for over 80% of the variance.

Conclusions: Our findings suggest that peripheral serum protein levels are associated with opioid-induced behavioral phenotypes, indicating their potential utility as biomarkers for predicting addiction-related behaviors.

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MIR-9 IS ASSOCIATED WITH COMPULSIVE AVERSION-RESISTANT ALCOHOL DRINKING IN MICE

Matar Levin Greenwald, Segev Barak, *School of Psychological Sciences, and Sagol School of Neuroscience, Tel Aviv University*

Objective: Alcohol Use Disorder (AUD) is a chronic, relapsing psychiatric disorder, characterized by out-of-control compulsive alcohol drinking, and an inability to reduce drinking despite negative consequences. Alcohol consumption leads to many brain neuroadaptations in the brain' reward system, including the striatum. Recently, microRNAs, have been implicated in regulating alcohol drinking. Here, we tested the involvement of microRNA-9 (miR-9) in compulsive aversion-resistant alcohol drinking in mice. Methods: We first established a mice model for compulsive aversion-resistant alcohol consumption. Mice consumed 10% or 20% alcohol, in a 4-week intermittent-access 2-bottle choice procedure. Then, alcohol was adulterated with escalating concentrations of quinine, and consumption was recorded. The levels of miR-9 in the dorsomedial striatum (DMS) were assessed following pretraining of alcohol drinking. Results: We found that quinine-adulteration reduced alcohol consumption in mice pretrained with 10%, but not with 20% alcohol solution, suggesting that 20% alcohol drinking induces compulsive-like alcohol consumption. miR-9 expression was reduced in the DMS of 20% , but not 10%, alcohol-drinking mice, suggesting its association with their differential drinking patterns. Conclusions: Our findings suggest that miR-9 may be involved in compulsive, aversion-resistant alcohol consumption.

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Cocaine differentially affects mitochondrial function depending on exposure time

Sahar Wattad1, Gaby2, Miri Shmuel1, Hannah2, Claire Thornton2 and Rami Yaka1
Hebrew University

Cocaine differentially affects mitochondrial function depending on exposure time Sahar Wattad1, Gaby2, Miri Shmuel1, Hannah2, Claire Thornton2 and Rami Yaka1 1Institute for Drug Research (IDR), School of Pharmacy, Faculty of Medicine, The Hebrew University of Jerusalem.2Department of Comparative Biomedical Sciences, Royal Veterinary College, London, UK. Objectives: The current study investigates the effects of repeated low-dose cocaine administration on mitochondrial dynamics and function in a neural cell line C17.2, highlighting differences between acute and chronic exposure. Methods: C17.2 mouse neural precursor cells were cultured in DMEM with supplements and exposed to cocaine (1-100 µM) over 4 weeks to assess chronic effects, with media refreshed multiple times per week. Reactive oxygen species (ROS) were measured using dihydroethidium staining and fluorescence imaging, while mitochondrial and nuclear imaging utilized Hoechst and Mitotracker dyes analyzed with confocal microscopy. Additional analyses included gene expression using qPCR, oxygen consumption rates with Seahorse assays, and statistical evaluations through ANOVA for significance. Results: A single exposure of cocaine induces oxidative stress and alters mitochondrial function, with significant superoxide production even at low doses by 24 hours. Repeated 3-day exposure reduces oxidative stress but does not affect cell proliferation, though mitochondrial bioenergetics show impaired spare respiratory capacity. After 4 weeks of chronic cocaine exposure, cells adapt, with no impact on survival or ROS production, and mitochondrial morphology remains unchanged across all conditions. Conclusions: Repeated cocaine exposure promotes cellular adaptations that preserve proliferation and enhance mitochondrial function, despite initial oxidative stress. This suggests a complex resilience mechanism in response to chronic drug treatment.

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Session 36

Psychiatric and neurodevelopmental disorders : PTSD

INDIVIDUAL BEHAVIORAL PROFILING AS A TRANSLATIONAL APPROACH TO ASSESS TREATMENT EFFICACY IN PTSD

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The first-line pharmacological treatments for PTSD patients are serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs). However, both treatments achieve full recovery in fewer than 30% of patients, underscoring individual responsiveness variability. To this day, there is a profound lack of knowledge regarding the neural mechanisms underlying responsiveness to these treatments.

Employing an animal model of PTSD with male rats, rats were differentiated into trauma-affected and unaffected individuals utilizing Individual Behavioral Profiling (IBP). Affected individuals were treated for one month with SSRIs or TCAs, thereafter, underwent additional behavioral evaluations and were differentiated into treatment responders or non-responders based on the IBP approach. Electrophysiological recordings (ER) and western blot analysis were conducted. Our findings unveiled differential responsiveness rates between treatments, mirroring the statistical rates observed in men with PTSD. ER data disclosed significant differences in local circuit characteristics between responders and non-responders to SSRI treatment. Western blot analysis revealed distinct patterns of GABA and NMDA receptors subunits expressions following both treatments, according to responsiveness.

The results, facilitated by IBP-based differentiation to responders and non-responders, suggest a modulation in the excitation-inhibition balance contingent upon treatment responsiveness. Moreover, they underscore differences in the underlying neural mechanisms associated with responsiveness to each treatment.

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Serotonergic modulation of dentate gyrus contribution to individual variability in response to stress

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Only a minority of individuals who experience trauma develop post-traumatic stress disorder (PTSD). This variability in stress-coping presents a challenge for addressing trauma-induced psychological disorders. The dentate gyrus (DG) has been identified as sensitive to stress characteristics, indicating its potential role in stress coping, with GABAergic interneurons being implicated in this process. The serotonergic projection to the DG targets mainly GABAergic interneurons.

The current study aims to manipulate serotonergic neurons projecting from the median raphe nucleus (MRN) to the DG and study the effects on individual variability in response to stress. Retro-AAV-CRE is injected into the DG, while AAV-DIO-DREADD is injected into the MRN of male rats, allowing selective manipulation of this pathway. Open field test, elevated plus maze, and a two-way shuttle avoidance task are examined to determine whether DG manipulation by serotonergic neurons affects stress-coping alterations.

In later stage, manipulating the functioning of subsets of GABAergic interneurons, by either EphA7 or Neurofascin knockdown, known to influence GABAergic synapses selectively at proximal dendrites and soma or the Axon Initial Segment (AIS), will be carried out in order to verify which GABAergic interneurons mediate the effects of the serotonergic projection to the DG in individual variability in response to stress.

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Neural Correlates of Trauma Experienced Under the Influence of Psychoactive Substances: Insights from the Supernova Festival Terror Attack

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5. SafeHeart NGO

Objectives: Traumatic events induce acute psychological, physiological, and neural responses and may lead to psychopathologies such as PTSD. Trauma exposure has been associated with alterations in functional connectivity within key brain networks, including the Default Mode Network (DMN), Salience Network (SN), and Central Executive Network (CEN). Specific regions, such as the amygdala, ventromedial prefrontal cortex (vmPFC), and hippocampus, show notable changes, including amygdala hyperactivity, vmPFC hyporeactivity, and altered hippocampal connectivity. This study examines the posttraumatic processing and neural correlates of survivors from the Supernova festival terror attack on October 7th, 2023, many of whom were under the influence of psychoactive substances, potentially affecting their psychological and neural responses.
Methods: Participants included festival survivors and controls with similar demographics. Participants underwent two 6-minute resting-state fMRI scans, before and after viewing a 6-minute movie depicting a similar music festival designed as a stressor. Inter-subject correlation analysis compared functional activity between control and experimental groups.
Results: Preliminary findings (n=86) revealed significant differences in neural activation patterns during the movie stressor, suggesting altered neural processing in survivors of the attack.
Conclusion: These findings provide novel insights into the neural correlates of trauma experienced under psychoactive substances, highlighting significant alterations in brain connectivity and activity.

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Topic 37

Psychiatric and neurodevelopmental disorders : Schizophrenia

3’-tRNA-Ala fragments guide nuclear MEG3 splicing linked to nonmotor dysregulation in Parkinson’s disease

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Nonmotor neurobehavioral impairments reshape quality-of-life years before Parkinson’s disease (PD) diagnosis, but the underlying molecular mechanisms remain obscure. Here, we report substantia nigra co-elevation of interacting non-coding RNAs, 3’end tRNA-alanine fragments (3’-tRFs-Ala) and the brain-specific splice variant of MEG3 lncRNA, in the late-stage of PD.
Linking the interaction to behavioral symptoms, the MEG3-long interacting region reflects sex-specificity of PD symptoms and coincides with the evolutionarily conserved miR-770-5p precursor site (pre-miR770) of MEG3-long variant associated to the murine social fear learning/behavior. Highlighting brain-immune system crosstalk, blood 3’-tRFs-Ala levels decline with nonmotor PD symptoms severity in human GBA+ mutation carriers whose PD and immune symptoms are more severe and emerge earlier than in mutation-free PD patients. Implicating simultaneous 3’-tRFs-Ala contributions to nuclear MEG3 splicing/pre-miR770 pre-processing and cytoplasmic translation of proteins involved in key nuclear processes, pull-down strategy identified 3’-tRFs-Ala-binding to numerous spliceosome-related and tRNA aminoacylation proteins and numerous mRNA targets. Moreover, 3’-tRFs-Ala ‘sponging’ in human neuroblastoma cells and decreased nuclear 3’-tRFs-Ala fraction under acute oxidative stress altered MEG3 splicing, unraveling novel PD pathology-related molecular mechanisms. Together, our findings reveal PD-neuropathology links to actively interrupted 3’-tRFs-Ala/MEG3-long interaction and behavioral impairments both in the early pre-motor and late disease stages, offering novel non-coding RNA roles to human brain function and cognition.

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UTILIZING ARTISTIC EXPRESSION FOR SCHIZOPHRENIA DIAGNOSIS THROUGH MACHINE LEARNING

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Schizophrenia, affecting cognition, perception, emotion, and social behaviors, notably influences patients' artistic output, manifesting unique characteristics. Given the limitations of current lengthy diagnostic methods with a 25% error rate, our study proposes a novel neural network model that classifies these artistic markers to assist in diagnosis. Our study involved 764 participants, with 45% diagnosed with schizophrenia.

All participants, aged 38.25 years on average (SD=13.43), with a 43.88% female representation, were tasked to create eight drawings of human faces. These drawings were digitized and classified based on schizophrenia status, forming the initial training dataset for our model. The data was processed using Python and converted into a NumPy array for input into our Keras library-developed model. The model's performance was evaluated using key metrics: Area Under the Curve (AUC), specificity, and sensitivity. On a new test dataset, the model demonstrated an AUC of 0.90, sensitivity of 0.84, and specificity of 0.85.

In conclusion, this methodology utilizing machine learning to analyze art created by schizophrenia patients shows promise for enhancing current diagnostic methods, potentially providing a faster, more accurate diagnosis, and personalized patient care. Future research will focus on model refinement across diverse populations and art forms.

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Behavioral assessment of cognitive models of schizophrenia using novel mouse CANTAB-like test batter

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Cognition is among the first domains to be affected in schizophrenia and can predict the onset of psychosis. Measuring cognitive changes in schizophrenia often involves a battery of multiple tests, where individual performance is compared to the average performance of the healthy population.

However, animal models usually focus on a single cognitive domain using a limited number of cognitive assays. In addition, behavioral analysis is performed at the group level without reference to individual variability. In the present study, we designed a battery of cognitive tests equivalent to a human CANTAB battery. This battery includes learning, memory, social behavior, problem-solving, and extra-dimensional set shifting assays. To assess the relevance of the battery to schizophrenia research, we tested glutamate dehydrogenase (Glud1)-deficient mice, previously shown to mimic schizophrenia-like phenotypes. The performance of each animal in each assay was compared to the average performance of a control group. Based on performance in several assays, animals were categorized into three groups: High-, Average- or Low-cognitive performers.

We found an unequal distribution of cognitive performance in the different genotypes tested. This indicates that the novel mouse CANTAB-like battery may be a useful tool for .the assessment of cognitive abnormalities in schizophrenia

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Glutaminase 1 Inhibition as a therapeutic venue in schizophrenia: intermin conclusions from a double-mutant mouse model

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Objectives: Hippocampal expression of the glutamate-catabolizing enzyme Glutamate Dehydrogenase 1 (Glud1 gene) is downregulated in schizophrenia. We previously showed that CNS-Glud1-/- mice show enhanced CA1 glutamate and schizophrenia-behavioral abnormalities, also present in CNS-Glud1+/- mice exposed to mild stress. Conversely, mice genetically modified to express less glutaminase-1 (Gls1 gene), which converts glutamine to glutamate, display reduced CA1 glutamate and resilience to schizophrenia-like abnormalities. Here, we created double-mutant mice heterozygous for both Glud1 and Gls1 mutations in CNS, to investigate if Gls1 deficiency mitigates CNS-Glud1+/- deficits.
Methods: CNS-Glud1+/-, CNS-Gls1+/-, CNS-Glud1;Gls1+/- (double mutants) and CNS-Cre+ Controls were exposed to mild stress and tested for behavioral abnormalities and changes in CA1 metabolomic profile.
Results: Female CNS-Glud1+/- mice displayed hyperactivity at baseline and after amphetamine (2mg/kg) administration, whereas CNS-Gls1+/- and double-mutant mice showed no increase in activity. Male CNS-Glud1+/- mice displayed baseline locomotor hypoactivity, absent in double-mutant mice. In the water-T-maze, double mutants displayed cognitive deficits. Metabolomic analysis revealed elevated glutamate in CNS-Glud1+/-, but not in CNS-Gls1+/- or double-mutant mice. Five additional metabolites were affected by genotype.
Conclusions: Glutaminase inhibition in CNS reverses some of the schizophrenia-like behavioral and metabolic abnormalities induced by Glud1 deficiency and may be a therapeutic venue.

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Brain-Wide Neuronal Networks in a Schizophrenia Mouse Model

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Schizophrenia is a severe mental-health condition that impacts the well-being of millions. While its association with abnormal neuronal activity in various brain areas is established, the dysfunction of brain-wide networks in schizophrenia remains largely unexplored. This study uses a specialized mouse model treated with MK-801 via miniosmotic pumps (SZ) to replicate aspects of the disorder and gain insight into its neurobiological mechanisms. We use advanced calcium imaging to compare brain-wide neuronal activity between wild-type (WT) mice and those with schizophrenia-like symptoms. Optic fibers are implanted in numerous brain regions, including the amygdala, hippocampus, and nucleus accumbens, to capture dynamic brain-wide networks during free movement. This multifiber photometry system allows us to observe neuronal interactions as mice perform behavioral tasks including anxiety assessments (EPM and open field), social interaction (3-chamber), and memory tests (novel object). Our primary goal is to identify differences in neuronal network patterns between SZ and WT mice. Initially, we observe significant behavioral differences in SZ mice that align with schizophrenia-related behaviors. Preliminary results reveal altered dynamics in several brain areas of SZ compared to WT mice. These findings aim to clarify how schizophrenia affects brain-wide neuronal dynamics, improving our understanding of the disorder and its neurobiological impact.

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Predictive Processing During Smooth Pursuit in Acute Psychiatric Patients

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Objectives: Previous research has established impairments in smooth pursuit eye movements (SPEM) among individuals with psychiatric disorders, particularly schizophrenia. While past studies employed global assessments, recent work has focused on quantitative approaches to identify specific altered components of smooth pursuit. This study investigates smooth pursuit abnormalities across acute and non-acute psychiatric conditions, emphasizing predictive mechanisms.

Methods: The study included 66 participants: 32 healthy controls, 13 patients with acute psychotic symptoms, 15 with chronic psychotic symptoms, and 7 with acute non-psychotic symptoms. Eye movements were recorded using a Tobii 4c eye-tracking system during smooth pursuit tasks tracking a target moving at 7 degrees per second in 8 directions, and occlusion tasks.

Results: Patients showed intact full pursuit speed and initial saccade characteristics comparable to controls. However, acute psychotic patients exhibited significantly larger tracking lag and slower smooth tracking components. During occlusion trials, controls anticipated target reappearance, while patients typically did not, showing significantly larger deviation. The occluder-induced deviation negatively correlated with positive symptoms but not negative symptoms.

Conclusions: Despite normal basic tracking speed, psychiatric patients demonstrated specific deficits in predictive tracking mechanisms. The correlation between tracking deviation and positive symptoms suggests these deficits might be potential diagnostic indicators.

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DREADD-induced inhibition of hippocampal (CA1) pyramidal neurons in C-Glud1 -/- mice

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Objectives: Previous research on pharmacological and genetic rodent models has shown that glutamate abnormalities, specifically elevated glutamate levels, are associated with a range of adverse outcomes, such as behavioral deficits and altered gene expression. Here, we aim to examine whether DREADD-induced inhibition of dorsal hippocampal (dCA1) pyramidal neurons can ameliorate these deficits.

Methods: The dCA1 subarea of the hippocampus of C-Glud1 -/- mice, or their Cre+ controls, were bilaterally injected with either inhibitory DREADD (hM4Di) or a control virus, and then underwent a behavioral battery. The battery included open field, social preference and recognition, puzzle box, water T-maze, and an amphetamine challenge. All mice were injected with CNO (1 mg/kg) 30 minutes before the behavioral tests.

Results: DREADD-induced inhibition of pyramidal neurons in C-Glud1 -/- mice attenuated the response to amphetamine, and normalized the deficit in the water T-maze.

Conclusions: DREADD-induced inhibition of dCA1 pyramidal neurons in C-Glud1-/- mice normalizes some of the behavioral deficits exhibited by the Glud1 deficiency, and suggests a role for glutamatergic signaling from dorsal CA1 in said behavioral deficits.

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Topic 38

Psychiatric and neurodevelopmental disorders : Stress

Regulation of the CB1 Receptor by Neurensin-2 in Depression

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Major depressive disorder (MDD) is a prevalent psychiatric condition with a significant global impact. Inhibition of cannabinoid receptor 1 (CB1R) has been long associated with both depression and anxiety disorders in yet unknown mechanisms. Recently, we identified a novel depression-mediating protein, Neurensin-2, which is expressed specifically in CCK inhibitory interneurons in the hippocampus, the same neurons that selectively express CB1R. Here, we demonstrate for the first time that Neurensin-2 regulates CB1R expression.

Neurensin-2 is a stress-responsive vesicular protein with a putative role in protein trafficking. Using RNA-sequencing in Neurensin-2 overexpressing N2A cells, we found downregulation of synapse-related genes. Specifically, we observed that the retrograde endocannabinoid signaling was downregulated and that the Cnr1 gene expression (encoding CB1R) was significantly attenuated. Biochemical analysis confirmed reduced CB1R mRNA and protein levels with Neurensin-2 overexpression, while Neurensin-2 knockdown increased Cnr1 expression. Additionally, in chronically stressed mice with high Neurensin-2 levels, Cnr1 expression was reduced, Furthermore, Neurensin-2 overexpression also downregulated CB1R downstream signaling pathways, including Akt, Erk1/2, and mTOR phosphorylation. Our results strongly suggest that stress-induced Neurensin-2 increases lead to CB1R downregulation, proposing a novel mechanism linking CB1R inhibition with depression and anxiety.

The newly identified interplay between Neurensin-2 and CB1R may offer valuable cell-type-specific insights for developing targeted therapies for depression and anxiety.

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Characterization of Neurensin-2 knock-out mice

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Major depression disorder (MDD) affects millions worldwide, yet its pathophysiology remains poorly understood. While some individuals are susceptible to developing depression, others show resilience. This study focused on Neurensin-2, a vesicular protein recently identified as a key mediator in depression, with its deletion conferring resilience to chronic stress.

We aimed to comprehensively characterize the basal behavioral effects of Neurensin-2 deletion in mice. Using Neurensin-2 knockout male and female mice, we examined the affect on cognitive, emotional, and motor performance. In addition, we investigated Neurensin-2's effects on body weight and stress-induced molecular changes, particularly focusing on the excitatory/inhibitory balance in the brain. We found that Neurensin-2 deletion confers basal anxiolysis and weight reduction without impacting cognitive, social, or motor functions.

Furthermore, knockout mice exhibited impaired hippocampal inhibitory transmission, which is resilient to the stress-evoked excitatory/inhibitory imbalance seen in wild-type mice. Our findings suggest that low levels of Neurensin-2 confer stress resilience by inducing basal anxiolysis and a shift in hippocampal excitatory/inhibitory balance.

These, without compromising cognitive function or gaining weight. Thus, we suggest that Neurensin-2 is an exciting potential drug target for treating depression and anxiety disorders as well as for promoting stress resilience.

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9CBC DECRASED THE EFFECTS OF SOCIAL ISOLATION STRESS

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Objective: Social isolation has been associated with poor physical and mental health status, as well as premature mortality, possibly due to increased inflammation, and stress hormones. Carotenoids and their derivatives reduce inflammation, and regulate the HPA axis. This research examined the effect of 9CBC from the alga Dunaliella bardawill on Tg2576 mice that were socially isolated.

Methods: We measured the mouse weight periodically, and recorded the mice mortality. In addition, we measured mice anxiety using the Open field test.

Results: Throughout the experiment, a gap between 9CBC-treated WT and WT control mice developed such that 9CBC-treated WT mice gained significantly less weight than the WT control group. In addition, Tg2576 mice have a survival rate of approximately 75%. In our study, the survival rate was lower - 45%. In contrast, 9CBC-treated Tg2576 mice had a significantly higher survival rate - 78% compared to the non-treated mice. Moreover, the Open field test exhibits less anxiety in 9CBC-treated Tg2576 mice.

Conclusions: Weight gain results together with the significantly higher survival rate in the 9CBC-treated Tg2576 group, suggest that 9CBC may have an effect on stress. This is consistent with our behavioral test results which indicated reduced anxiety due to 9CBC treatment.

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The Impact of THC on Neurogenesis and Stress Response: An In Vitro Investigation In Astrocytes

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Noam Shomron, *Tel Aviv University*

The Impact of THC on Neurogenesis and Stress Response: An In Vitro Investigation In Astrocytes Objectives To investigate the intricate relationship between adult hippocampal neurogenesis, stress, and delta-9-tetrahydrocannabinol (THC).

We aim to uncover THC's potential in mitigating stress-induced gene expression changes in astrocytes and promoting neurogenesis. Methods We induced cellular stress in an astrocyte-derived glioblastoma cell line through serum deprivation and subjected primary hippocampal mouse astrocytes to psychological stress using glucocorticoid treatments. THC's impact on astrocytic stress responses and neurogenesis was examined. Stress responses were measured through gene expression analysis using real-time quantitative PCR. Results Preliminary findings indicate that THC enhances the viability of stressed astrocyte-derived glioblastoma cells without affecting non-stressed cells.

THC-treated stressed cells showed increased expression of BDNF and decreased levels of FGF2 compared to non-stressed cells. These results suggest a targeted influence of THC on neurogenesis. Additionally, THC appeared to modulate the astrocytic stress responses effectively, promoting the support of neurons during neurogenesis. Conclusions THC seems to have a specific impact on stressed astrocytes, promoting neurogenesis and potentially offering therapeutic benefits for stress-related disorders.

Further analysis of THC's effects under psychological stress conditions in primary mouse astrocytes will elucidate its mechanisms of action.

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NEWBORN REACTIONS TO MATERNAL PRENATAL STRESS ALTER UMBILICAL CORD BLOOD TRNA FRAGMENTS TARGETING CHOLINERGIC TRANSCRIPTS

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Maternal perceived prenatal stress (PPS) is a known risk factor for diverse developmental impairments in newborns, but the underlying molecular processes are

incompletely understood. Here, we report that PPS responses altered profiles of blood transfer RNA fragments (tRFs), 16-50nt long non-random cleavage products of tRNAs at birth. Moreover, maternal and umbilical cord serum from stressed and control mothers and their newborns presented selective enrichment of particular tRF families grouped by their mitochondrial or nuclear genome origin, coded amino acid and cleavage type.

Suggesting a sex-specific effect, grouped tRF families revealed shared length and expression patterns which were strongest in the female newborns. Of those, some tRFs carried complementary motifs to specific cholinergic mRNAs, indicating possible translational regulation similarly to microRNAs.

Compatible with the cholinergic regulation of stress reactions, those "CholinotRFs" achieved AUC of 95% when classifying female newborns according to maternal PPS. Correspondingly, we found altered catalytic activity of serum acetylcholinesterase, an effect which was elevated in male newborns, marking a second sex-specific impact.

Our findings indicate association of tRF families' patterns with newborns sex-specific stress response to PPS, and may lead to better diagnosis and therapeutic tools for these and other stressors.

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Social and Metabolic Stress in Adolescent Female Rats Induces Divergent Gene Expression and Behavioral Outcomes Across Generations

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Inna Gaisler-Salomon, *School of Psychological Sciences; The Integrated Brain and Behavior Research Center (IBBRC), University of Haifa*

Objectives: Stress has behavioral and physiological consequences across generations, yet few studies have examined its impact on adolescent females. This study aims to investigate whether exposure to social or physiological stress during adolescence affects behavior and transcription levels of Oxytocin (OXT), Oxytocin Receptor (OXTR), Corticosterone and Corticosterone Release Hormone Receptor 1 (CRHR1), and miR34c in blood serum, brain and oocytes. Additionally, we asked whether maternal stress exposure affects the behavior of stress-naïve offspring.

Methods: Adolescent female rats underwent social isolation (SI) or Food and Water Deprivation (FWD) stress for 7-days. Two weeks later, they were tested for behavioral abnormalities, gene and miRNA expression. Behaviorally-naïve females were mated with naïve males. First (F1), second (F2), and third (F3) generation offspring were tested for behavioral alterations.

Results and Conclusions: Both stressors led to anxiety-like behavior and elevated NAc Crhr1 mRNA. However, only SI induced depression-like behavior, increased PVN Oxtr and elevated CORT and OXT levels in blood. SI-stress alone altered Crhr1 and miR34c expression in oocytes and affected brain Crhr1 expression and social recognition in F1 and F2 offspring. Notably, neither stressor changed maternal care. Future studies may explore the mechanisms involve in the transgenerational transmission of social behavior.

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The biological mechanism behind the anti-depressant effect of Shan-Zha in mice

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Depression and anxiety pose significant challenges to mental health worldwide. While selective serotonin reuptake inhibitors (SSRIs) have been the standard choice for antidepressant treatment, they often exhibit limited efficacy and unwanted side effects, including decreased libido and weight changes.

In search for alternative solutions, we recently published that Shan Zha (Israeli Patent No 275222) is sufficient to produce an anxiolytic and antidepressant-like effect similar to Escitalopram without affecting the serotonin transporter and with activation of the 5-HT1A serotonin receptor. Notably, the Shan Zha group did not exhibit the common side effects of decreased sexual function and weight changes. The current study explores the antidepressant effects of Shan Zha, a traditional Chinese herb, aiming to understand its biological mechanism.

The primary research question is to elucidate the biological mechanism behind the absence of side effects in Shan Zha compared to SSRIs, focusing specifically on noradrenaline and dopamine markers. 1-month-old male ICR mice were subjected to 4 weeks of unpredictable chronic mild stress (UCMS) and treated with either Saline, Escitalopram or Shan Zha for 3 weeks. 24 hours after the last treatment, mice were examined for depressive and anxiety-like behaviors as well as side effects. Following the behavioral examination, the hippocampus and prefrontal cortex were extracted.

We measured neurotransmitters (dopamine and noradrenaline), their breakdown substances, and receptors using HPLC and RT-PCR methods. The findings indicated that, unlike SSRIs, Shan Zha primarily influences the dopaminergic and noradrenergic systems. The absence of side effects may be attributed to this specific focus on these pathways.

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The Impact of Cognitive Behavioral and Mindfulness Intervention on Gut-Immune-Brain Interactions in Crohn's Disease

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7. Dept. of Gastroenterology and Hepatology, Soroka Medical Center

Crohn's disease (CD) involves chronic stress and inflammation along with microbiome and metabolic changes. Our research showed that a 3-month trial of cognitive behavioral and mindfulness daily exercise (COBMINDEX) improves the well-being of CD patients, associated with changes in systemic inflammation and microbiome profiles. We hypothesize that COBMINDEX impacts immune regulation via rebalancing the microbial composition.

CD patients were analyzed for distress, well-being, microbiome, and immune profiles at recruitment and 3-months post-intervention and categorized into Top-Responders (TRs) and Poor-Responders (PRs) based on psychological surveys. PBMCs were analyzed by flow-cytometry for CD4 T-cell subsets. Serum samples underwent metabolomics analysis using LC-MS. Compared with PRs, frequencies of exhausted, effector memory, and regulatory CD4 T-cells were decreased in TR, along with increased frequencies of naïve T-cells. Metabolomics profiling of serum samples showed distinct patterns between TR and PR individuals such as the PR group had higher levels of the secondary bile acids Tauroursodeoxycholic Acid and Fructoselysine.

Overall, both the landscape of CD4 T-cells and the metabolite profile in the TR group exhibited a greater similarity to healthy controls. These observations highlight the potential of COBMINDEX to alleviate the pathology of CD via microbiome-derived metabolites that can impact the inflammatory properties of T cells.

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Resting Under Stress: How War Stress Affects Brain Networks Supporting Executive Functions Networks in Children

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Environmental stress, especially in children, is linked to emotional stress and reduced cognitive control abilities (i.e., executive functions (EF) and high alertness levels). War-related events are environmental stressors; however, the connection between the number of such events and functional connectivity in attention and EF remains unclear. Additionally, war events may affect academic abilities, which rely on cognitive and attention skills.

This study assessed the impact of war exposure on children's academic performance using Resting-state (RS) functional connectivity. In this study, 17 Israeli children (aged 8–15) were scanned during the October 7th war (January–July 2024). Within and between functional connectivity, data was exported from neural networks supporting EFs and attention abilities (fronto-parietal, cingulo-opercular, ventral, and dorsal attention) and reading (auditory and visual networks).

War-related events were measured via a personalized questionnaire, and reading skills were evaluated. Pearson correlation analysis revealed a positive link between functional connectivity within the dorsal and ventral attention networks and exposure to war events related to reduced reading skills.

The results suggest that heightened exposure to war-related events is linked to neurobiological changes tied to increased alertness and decreased academic performance, highlighting the need for educators and decision-makers to address the impacts of environmental stress on learning.

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Topic 39

Reward system

Hippocampal reward location encoding in a non-spatial environment

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It has been shown that beyond their homeostatic functions, astrocytes serve as active regulators of synaptic transmission and plasticity, and have pivotal roles in information processing. Interestingly, recent work from our lab (Doron et al., Nature, 2022) has found that astrocytes ramp up their calcium levels when a water-deprived mice approached a water reward in a familiar virtual reality environment, under a two-photon microscope.

This effect was not found when the reward moved to another location in the environment, or when the mouse ran in a novel environment. These findings raise the question of whether astrocytes encode the reward itself or its location, so we decided to test if astrocytes react in the same manner to a reward in a non-spatial environment. For that purpose, we injected mice with AAV5-GFAP-GCaMP6f and implanted cannulas over their CA1, allowing investigation of hippocampal astrocytic calcium elevations.

We then trained the mice to run in a non-spatial, auditory, environment (e.g. series of 12 pure tones with elevating pitch) and scanned their CA1 astrocytes. We hypothesize that astrocytes would elevate their calcium activity in the presence of a reward in a familiar auditory environment. This might broaden the known astrocytic role in reward location encoding.

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Motivation and Operant Learning in Drosophila: Insights from the FlyPAD / OptoPAD System

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Motivation is a neuronal representation of internal states that drive goal-directed behaviors. Once the goal is reached, the brain reward system positively reinforces the behavior by coupling it to a pleasurable feeling.

In Drosophila, the Neuropeptide F system (NPF, the fly homolog of mammalian NPY) regulates motivated behaviors and reward. As such, activation of NPF neurons induces appetitive memories. Here we employed a two-choice optogenetics-based operant learning paradigm, in which single flies learn to self-stimulate their NPF neurons by touching an electrode that is coupled with optogenetic stimulation. We provide evidence that the neuropeptide NPF is necessary for the development of preference towards the activating electrode, as its K.D. abolishes learning. We used this system to explore the way by which motivational states, prior experience, and sex shape learning kinetics.

We discovered that female flies show faster learning with fewer touches on the non-illuminating electrode compared to males, suggestive of a difference in their learning strategies, and that social isolation reduces learning capacity in male flies. Our experimental paradigm offers a valuable tool to dissect the circuitry process reward within the fly brain and to investigate mechanisms encoding changes in motivational states.

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Distinct dopamine signaling in the striatum and frontal cortex during reward processing

Yirat, Henshke, *the Hebrew university*
Eran, Lottem, *the Hebrew university Mati, Joshua, the Hebrew university*

Dopamine (DA) is crucial for processing reward, motivation, and motor control. Its importance is underscored by severe conditions such as Parkinson's disease, depression, and addiction, which arise from dopamine depletion or imbalance. Despite this, real-time measurements of DA activity during behavior have been challenging. In this study, we measured dopamine with fiber photometry which allowed us to measure DA levels with sub-second resolution in behaving monkeys. We focused on the striatum and frontal cortex—two key regions implicated in reward processing and decision-making.

Our findings reveal distinct differences in DA signaling between the striatum and frontal cortex during tasks that manipulate reward probability and size. In the striatum, DA responses aligned with the reward-prediction error theory: activity increased during the cue phase with larger, more certain rewards and is strongly elevated during reward delivery for probabilistic but not certain rewards.

Conversely, DA activity in the frontal cortex predominantly responded to reward-predicting cues, with sustained activity during the cue phase that correlates with anticipated reward value but showed minimal modulation at reward delivery. These cortical responses align with reward expectation rather than reward prediction error, suggesting a distinct function in reward processing. Overall, our results provide critical insights into DA's role across brain regions, underscoring the importance of region-specific DA signaling in shaping reward-driven behavior.

This study's novel approach for measuring dopamine in monkeys offers valuable tools for further exploration of DA's role in complex behaviors, with potential implications for understanding and treating DA-related disorders.

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ARE ALL VENTRAL PALLIDUM PROJECTIONS MADE EQUAL?

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Tal, Odesser, *Herbrew University Shana, Golden, Hebrew University*
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The Ventral Pallidum (VP) is a key region in the brain's reward system, mediating motivated behaviors and addiction. Despite its relevance to psychiatric disorders, the specific roles of VP projections remain underexplored. This study systematically characterizes the four main VP projections—to the ventral tegmental area (VTA), medial dorsal thalamus (MDT), lateral hypothalamus (LH), and lateral habenula (LHb)—and their differential inputs from the Nucleus Accumbens (NAc) in naïve and cocaine-withdrawn mice. Using a combination of retrograde tracing, electrophysiology, optogenetics, and chemogenetics we reveal that VP projections differ in their intrinsic excitability, synaptic input patterns, and responses to cocaine withdrawal. During cocaine-conditioned place preference, inhibiting VP-VTA neurons increased preference scores, while inhibiting VP-LH neurons decreased them.

Moreover, cocaine withdrawal altered excitability in a projection-dependent manner, with VP-VTA neurons exhibiting changes contingent on their D1- or D2-MSN inputs. VP-LH and VP-LHb projections also displayed opposite synaptic adaptations following withdrawal.

These findings underscore the functional specialization of VP projections in reward processing and addiction. This projection-level resolution offers avenues for targeted therapeutic strategies to address addiction and other motivational disorders.

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Topic 40

Sensory systems : Attention

Utilizing Mobile Neurotechnologies to Investigate Students' Attention in School

Ofek Ben-Abu, Yuval Cohen, Renana Vaknin-Harel, Danna Pinto, Paz Har-Shai Yahav, Orel Levy, Samuel Mirsky, Adi Korisky and Elana Zion-Golumbic

Effective learning depends on students' ability to maintain attention and minimize distractions. However, most attention research occurs in controlled lab settings, lacking real-life relevance. Our study addresses this gap by investigating students' attention in the school environment using mobile neurotechnologies and cognitive experiments. Collaborating with "Begin" high school in Ramat Efal, we conducted experiments with 9th-grade students in their own classroom.

The study comprised two sessions: EEG and cognitive-testing. The EEG sessions were conducted in pairs and students wore portable 16-channel EEG. Two experiments were conducted: an auditory oddball task assessing neural responses to stimuli and task relevance, and a selective-attention classroom-learning experiment when the students were tasked to pay attention to a recorded lecture and answer comprehension questions about its content.

Distractors sounds were presented at random times throughout the experiment, alongside the naturally occurring distractors of the real-life classroom environment (e.g. construction noise, etc.). The cognitive-testing sessions included validated tasks on attention and executive functions. Students also completed questionnaires on demographics and ADHD symptoms. By bridging lab-based research with real-life education, our study contributes to understanding attention in educational contexts. Findings may inform personalized neuroeducational approaches and reveal connections between attentional abilities, neural patterns, and academic performance.

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The impact of noise on neural and physiological responses, in a Virtual-Reality classroom

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Listening and understanding a lecture in a noisy classroom or conference hall can be extremely difficult, as background noises mask the lecturer's speech and can distract attention. We used a novel VR experimental setup simulating a Virtual Classroom, to investigate the effect that different types of sounds and background noises on behavior, neural processing, eye movements and physiological responses.

In two experiments we investigated the impact of continuous and intermittent construction background noise, and of occasional transient auditory events such as ringtones and coughs, in individuals with ADHD and their matched controls. In Experiment 1 we find that intermittent background noise reduces neural tracking of the teacher's speech, increased physiological arousal, and impaired behavioral performance. Continuous noise, however, didn't show the same effects. In Experiment 2, we replicate the detrimental effect of background sounds on neural tracking of the teacher's speech, and demonstrate clear neural and physiological responses to background events.

Notably, neural and physiological response to background sounds were larger in individuals with ADHD. These results expand our understanding of how the brain processes speech-in-noise under realistic contexts, and exposes important variability between individuals in their ability to maintain attention in noisy places and their sensitivity to irrelevant sounds.

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Engagement of Attention, EF, & Sensory Processing Networks During Parent Story-Listening: an fMRI study

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Objective: This study examined neural circuits involved in future reading (attention, EF, language processing, and visualization) when children listened to stories narrated by a parent versus a stranger. We aimed to assess how attention, EF, and sensory systems were engaged during parental story-listening, and their relation to joint reading quality and future reading readiness.

Methods: Twenty-six Hebrew-speaking children ages 5.0-7.11 and their parents participated. We evaluated pre-literacy skills, cognitive abilities, and home literacy environment. Parents completed questionnaires about their and their child's cognitive control and language skills. Functional MRI data captured brain activity while children listened to stories narrated by their parent and a stranger. We analyzed functional connectivity in networks associated with attention, EF, language, and visualization, correlating these with behavioral measures of pre-literacy skills and HLE.

Results: Narrative comprehension scores were unaffected based on storyteller. However, children showed increased functional connectivity in sensory and EF-attention networks when listening to a parent, correlating with better language skills. **Conclusions**: Enhanced home reading time fosters engagement in EF and language processing, highlighting parental storytelling's role in developing future reading-related networks.

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Pre-microsaccade modulation in foveal V1: enhancement in the current and future stimulus locations

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2Equal contribution

Microsaccades are miniature saccades performed during visual fixation that were shown to play a pivotal role in active sensing. Recent studies suggested that pre-microsaccade attention may underlie the enhanced visual processing at the stimulus site.

However, the neuronal mechanism underlying this phenomenon at the foveal scale remains unknown. Using voltage-sensitive dye imaging we investigated the neural responses to uninstructed, spontaneous microsaccades in the fovea of the primary visual cortex (V1) in monkeys. We found that the neuronal activity at the current and future landing stimulus sites was enhanced before a microsaccade onset toward a stimulus. This enhancement was spatially confined to the current and future landing stimulus sites, which appeared to merge along the microsaccade trajectory in V1

Finally, we found a pre-microsaccade increased synchronization at the current stimulus site. Our findings shed new light on the neural modulations preceding microsaccades and suggest a link to neural signatures of attention.

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Topic 41

Sensory systems : Auditory

Neural correlates of auditory category learning of FM sweeps in the mouse auditory cortex

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Background and methods: Category learning is a fundamental brain process that enables quick and accurate response for novel stimuli in complex sensory scenes. The process has been shown to be accompanied by changes in neuronal representation, but the contribution of these changes to behavior are not yet clear. We trained mice to discriminate between two categories: rising frequency modulated (FM) sweeps and falling FM sweeps. We performed electrophysiological recordings from the auditory cortex of awake, expert and naive mice, while listening passively to FM sweeps and pure tones.

Results: At the end of training, we presented mice with novel stimuli and found that they the used frequency content of the sweep as the categorical boundary cue, rather than the slope of the sweep. We recorded single unit spiking activity from primary auditory cortex and the auditory temporal association cortex and found that more neurons of expert mice prefer the frequency of the category boundary comparing to naïve mice.

Furthermore, single neurons of expert mice as well their population activity have higher discriminability between sets of both FM sweeps and pure tones.

Conclusions: Our results show that plastic changes in the auditory cortex correspond to the behavioural strategy used by mice.

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Topic 42

Cortical and hippocampal circuits in Navigation

NEURAL REPRESENTATION OF HEAD DIRECTION IN THE DORSAL THALAMUS OF JAPANESE QUAILS

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We recently discovered head direction (HD) cells in the hippocampal formation (HPF) of an avian species - the Japanese quail (Coturnix japonica). In mammals, the HD signal requires vestibular and visual inputs to be integrated by a feedback loop between the lateral mamillary nucleus (LMN) and the dorsal tegmentum nucleus. From the LMN the flow of information is unidirectional conveying HD signal to the HPF through the Anterior Dorsal Thalamus.
We ask if birds have a homologue pathway. Towards this goal, we applied the Neuropixels recording technique in freely behaving quails. A deep learning-based video processing algorithm (DeepLabCut) was used to track the quail's body position and head direction. To target thalamus and hypothalamus for implantation, we developed an MRI based stereotaxic surgery.
Thus far, we have recorded from the dorsal thalamus of two quails. We identified a significant number of HD cells suggesting that in birds, likewise mammals, the dorsal thalamus plays a role in the generation of HD cells.
Further studies will be conducted to record from other regions in the putative HD network of the quail. The study provides insights into spatial coding in birds helping to better understand the evolution of the hippocampus and spatial coding.

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The Sensitivity of Auditory Cortex to Statistical Regularities

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Neurons in auditory cortex are sensitive to the probability of occurrence of sounds, to the order in which sounds are played, and even to more subtle statistical regularities of tone sequences. Magnetoencephalography (MEG) studies have provided compelling evidence that auditory cortex possesses a remarkable ability to efficiently discriminate between sequences with different levels of statistical regularities.

In order to examine this phenomenon at the level of single neurons, we recorded responses from auditory cortex of awake rats using neuropixels electrodes. The rats passively listened to multitone sequences. We describe here phase sensitivity - sensitivity to the position of sounds within repeated cycles of 4-6 tones which are the building blocks of the sequences. Each cycle contained the same tone frequencies, but the order within cycle ranged from fixed to random in different sequences. Surprisingly, we found phase sensitivity even in the most random condition that maintained cycles.

We conclude that the auditory cortex recognizes the sub-units from which the sequence is formed and is sensitive enough to detect extremely subtle statistical regularities.

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STIMULUS-SPECIFIC ADAPTATION (SSA) TO PURE TONES IN LOCAL NETWORKS OF MOUSE AUDITORY CORTEX

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Israel, Nelken, Edmond and Lily Safra Center for Brain Sciences Hebrew University

Stimulus-specific adaptation (SSA) is reduction in responses to a common stimulus that does not generalize, or only partially generalizes, to other, rare stimuli. SSA has been proposed to be a correlate of 'deviance detection', measured in EEG of humans as mismatch negativity (MMN), which peaks ~150–200 ms after the deviance point. One obvious difference between SSA in single cells and MMN is their time course. SSA 'rides' on the early cortical responses to sounds, whereas MMN occurs almost 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 true deviance sensitivity at about 100-150 ms after stimulus onset. These signals are believed to reflect the average spiking activity of a local network of hundreds of cells. To study the single-neuron activity that underlies the population responses, we used two-photon microscopy. We can resolve tens to a few hundreds of neurons with auditory sensitivity.

Many of these neurons showed late components in their calcium responses. The late components of these neurons were highly variable. We suggest that the reproducible late responses observed in the population reflect the activity of neuronal ensembles whose membership varies between trials.

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When do we hear?

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The perceptual center (P-center) of a sound is defined as the specific moment in time at which the sound is perceived to have occurred. Previous studies have shown that the behavioral variability in the p-center is affected by sound architecture, proficiency in music, task, and many other factors.

Though these studies probed the behavioral phenomena, they did not relate perception to the neural mechanisms underlying them. Here, I would like to investigate the neural mechanisms involved in the recognition of the perceptual centers, along with the temporal dynamics of these processes. Our preliminary data show that the P-center of different sounds is reflected in the latency of the N1 component in ERPs.

This is a promising indicator that the p-center variations result from variations in the time of the auditory processing. In my research, I would like to model how different physical features of sounds, as well as their sequential context, affect the latencies of the received ERPs. In addition, I would like to study the effects of learning and expertise on the p-centers. I will test whether familiarity with a sound leads to earlier p-centers.

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Topic 43

Sensory systems : Chemosensation

Enhancing Odor Separation: Intraglomerular Excitation and Interglomerular Inhibition

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Objective: Discrimination between similar sensory inputs is essential for animals' survival, and pattern decorrelation is crucial in achieving this ability. Pattern decorrelation reduces the overlap between neuronal patterns generated by similar sensory inputs. This study examines how intraglomerular interactions, mediated by muscarinic type B receptors (mAChR-B) expressed in olfactory receptor neurons (ORNs), contribute to pattern decorrelation and odor discrimination in the Drosophila olfactory system.

Results: We analyzed the Drosophila brain connectome and identified strong intraglomerular axo-axonal connections mediated by mAChR-B in ORNs, suggesting local circuit interactions. Surprisingly, mAChR-B exhibited an excitatory effect on ORN activity, selectively enhancing responses at high firing rates—this enhanced decorrelation of neuronal patterns for different odors. mAChR-B knockdown increased odor response correlation and impaired odor discrimination. Combining interglomerular inhibition through GABAergic receptors with mAChR-B-mediated intraglomerular excitation contributed to pattern decorrelation.

Conclusions: Our study reveals a novel mechanism in Drosophila's olfactory system where mAChR-B-mediated intraglomerular excitation enhances neuronal activity and facilitates odor discrimination. These findings expand our understanding of sensory systems, emphasizing the importance of intraglomerular interactions in sensory processing. The interplay between intraglomerular excitation and interglomerular inhibition provides a comprehensive mechanism for enhancing pattern decorrelation, facilitating precise odor discrimination in Drosophila.

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CIRCUIT LATERALIZATION AND ASYMMETRICAL MULTISENSORY INTEGRATION IN THE BRAIN OF C. ELEGANS

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The C. elegans nervous system exhibits overall bilateral symmetry, yet incorporates also asymmetry that promotes specialization and parallel processing, such as in certain sensory neurons. However, little is known about asymmetries in other neural circuit components, including interneurons.

We thus focused on the RIM interneuron pair, which is involved in sensory integration of conflicting stimuli. To assess the importance of the functional asymmetry in these neurons, we imposed symmetry by generating transgenic worms with artificially inserted gap junctions between the left and right interneuron pair. The effects on sensory integration were examined, revealing defects in sensory integration of two conflicting stimuli, without altering the response to either individual stimulus.

This suggests that the RIM interneuron pair acts asymmetrically in multisensory integration. We hypothesize that differential activation of the interneuron pair enables larger dynamic range compared to uniform activation. To test our hypothesis, we used calcium imaging to monitor RIML vs. RIMR neuronal activity and applied additional genetic tools to functionally segregate the left and right neurons. Results of this study will shed light on the effects of interneuron asymmetry and provide insights about overall structure-function relations in the nervous system.

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Cortical representation of olfactory stimuli during active behavior

Michael Yunerman *HUJI*,
Tamar Licht, *HUJI,*
Dan Rokni, *HUJI*

The piriform cortex (PCx) is the largest and most prominent part of the olfactory system that is believed to be indispensable for proper odor sensation. Despite extensive research, much remains unknown about the processing that olfactory information undergoes within the PCx.

In this study, we assessed whether the behavioral significance of olfactory stimuli is encoded in the PCx. We recorded the extracellular activity of PCx neurons, in awake and behaving mice that performed an olfactory odor detection task in which a conditioned stimulus (an odor of interest) was masked by other, nonsignificant, odorous stimuli.

We analyzed whether the statistics of responses to target odors differ from the responses to other odors. Additionally, we used decoding analyses to ask whether target odors can be more accurately decoded from the activity of PCx neurons compared to other odors.

Lastly, we asked whether how the engagement in the behavioral task affects our findings.

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AN UNDERSTUDIED NUCLEUS CONNECTING OLFACTORY BRAIN REGIONS WITH AMYGDALAR NUCLEI

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Dan Rokni, *Department of Medical Neurobiology, School of Medicine, The Hebrew University of Jerusalem.*

The olfactory system is known to be a strong modulator of emotional experiences and to support emotional memories.
This is typically attributed to the immediate connections between olfactory brain regions and the amygdala; however, these connections have been little studied. One main pathway that connects olfactory brain regions with amygdalar nuclei is via the nucleus of the lateral olfactory tract.
This nucleus combines features of both olfactory cortex, and amygdala, yet it's function and physiology are largely unknown. Here, we describe the biophysical and synaptic properties of nLOT neurons in acute slices.
We used optogenetic stimulation of individual input sources including the olfactory bulb, tenia tecta, piriform cortex, and the basolateral amygdala, and recorded postsynaptic responses. We show that nLOT neurons are bursters and that voltage gated calcium currents underly this property. nLOT neurons receive strong inputs from olfactory cortical regions as well as from the basolateral amygdala, yet only weak input from the olfactory bulb.
The stronger inputs can efficiently drive bursting in nLOT neurons.

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TESTING THE EFFECTS OF BREATHING PATTERNS ON COGNITIVE FUNCTION, EMOTIONAL PROCESSING, AND BRAIN ACTIVITY IN MICE

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Objectives: This research aimed to investigate the effects of various breathing patterns on cognitive function, emotional processing, and brain activity in mice. By training mice to modify their breathing, the study evaluated the resulting changes in cognitive performance, anxiety levels, and neural activity.

Methods: An experimental system recorded and analyzed breathing patterns in real-time. Mice were trained to control their breathing using light-based feedback. Cognitive function was assessed through sensory discrimination tasks, while behavioral tests evaluated social function and anxiety. Brain activity was measured in relevant regions to detect the neural correlates of altered breathing.

Results: The breathing training paradigm induced immediate and long-term effects on mouse physiology and behavior. Mice trained in slow breathing demonstrated improved cognitive performance compared to controls. Analyses of brain activity revealed neural mechanisms by which respiration modulated cognitive and emotional processes.

Conclusions: This approach combining breathing training, behavioral assays, and neural recordings uncovered the benefits of controlled breathing. The findings could open the way for novel, non-pharmacological interventions targeting cognitive and mental health in animal models and humans.

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Mapping The Inputs to the Nucleus of the Lateral Olfactory Tract (NLOT)

Aya Dhamshy, *Dr. Dan Rokni, Dr.Tamar Licht*

The nucleus of the lateral olfactory tract (NLOT) is a small nucleus located on the ventral surface of the brain within the amygdala complex.

The NLOT is of particular interest due to its connections with the olfactory bulb, which is responsible for relaying olfactory information, and its potential role in processing sensory input. Previous studies have revealed projections from the NLOT back to the olfactory bulb, suggesting the existence of a feedback loop that could modulate olfactory processing.

However, the specific functions and contributions of the NLOT to neural circuits and behavioral responses remain poorly understood.

In this study, we utilized a modern viral tracing method to map the inputs to the NLOT, aiming to provide a more detailed understanding of its connectivity and role within the brain's olfactory pathways.

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Topic 44

Sensory systems : Other

MAPPING NEURONAL REPRESENTATIONS OF PERIPHERAL IMMUNE RESPONSES

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Itay Zalayat, *Technion, The Ruth and Bruce Rappaport Faculty of Medicine Re'ee Yifa, Technion*
Tom Haran, *Technion, The Ruth and Bruce Rappaport Faculty of Medicine*
Rita Sirokin, *Technion, The Ruth and Bruce Rappaport Faculty of Medicine*
Hilla Azulay-Debby, *Technion, The Ruth and Bruce Rappaport Faculty of Medicine*
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The immune system is essential for maintaining homeostasis and responding to pathogens. Increasing research demonstrates the brain's role in encoding immune information and regulating its responses.
We recently identified the insular cortex as one brain region capable of these functions. However, the specific neuronal circuits and the peripheral information involved in this communication are still poorly understood. This research aims to uncover the neuronal representations of peripheral immune responses to better understand how the immune system communicates with the nervous system and what information is conveyed.
We used a combination of techniques, including whole-brain clearing and viral tracing of TRAPed (targeted-recombination-in-active-populations) neurons during peripheral inflammatory paradigms, to study the neuronal representations of immune activity. Preliminary results show specific neuronal circuits that change during a peripheral immune response.
In particular, projections to and from sensory, attention and memory-related brain regions connecting to the insular cortex are reduced during inflammation, while projections from the insular cortex to numerous amygdala areas and autonomic centers are increasing. By further interrogating these circuits, these findings will provide new insights into how the brain represents immunity.

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The role of thalamic visceral-sensory inputs to the insular cortex in need-driven behavior

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Yoav Livneh, *Department of Brain Sciences, Weizmann Institute of Science.*

Basic physiological needs such as hunger and thirst create powerful motivations that drive behavior, yet the underlying neural mechanisms remain unclear. The insular cortex (InsCtx), which encompasses the primary interoceptive cortex, integrates external cues with internal sensory information thought to be relayed from visceral sensory thalamic nuclei. However, direct evidence of visceral thalamus' involvement in interoception and need-driven behavior is lacking.

Here, we explore the role of visceral sensory thalamic inputs to the InsCtx by characterizing the information these inputs provide InsCtx during different physiological states, using fiber photometry and two-photon imaging.

Additionally, we assess their necessity for need-driven food or water consumption during hunger or thirst states using optogenetic inhibition. We find thalamic representation of predictive cues, reward delivery, reward consumption, satiation level, and prediction errors.
Optogenetic inhibition of these projections during need-driven behavior prevents behavioral manifestation of satiation by maintaining high motivation to consume food and water rewards, suggesting the critical role of thalamic projections in satiety.
We are currently establishing an experimental system to examine the role of cortical feedback within thalamocortical loop between the visceral thalamus and InsCtx.

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Non-invasive optogenetic interrogation of internal sensations and predictions

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Interoception, the perception of internal bodily signals, is crucial for brain-body communication, yet remains poorly understood due to limited tools for manipulating specific internal sensory systems.

To address this gap, we developed a novel approach combining optogenetic stimulation of internal sensing with behavioral paradigms and neural recordings in mice. We used this approach to non-invasively activate nutrient sensing intestinal cells, and vagal sensory neurons, initially validated using vagus nerve electrophysiology. We further used fiber photometry to find that stimulation of sugar-sensing intestinal cells and vagal neurons activated the nucleus of the solitary tract (NTS), a brain-stem region receiving interoceptive vagal input.

We then used this system to establish a behavioral task, in which mice associate external cues (e.g., smells, tastes) with optogenetic activation of specific internal stimuli, while recording NTS activity and midbrain dopamine signals. Activation of intestinal sugar sensing cells and vagal neurons enhanced artificial sweetener consumption and biased behavioral choice. We are currently investigating the creation and violation of internal predictions, while also examining related dopamine signals.

Looking ahead, we aim to use this experimental system with models of eating disorders (e.g., anorexia nervosa, obesity) to test the contribution of aberrant interoceptive signaling and interpretation of interoceptive signals

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Individual Differences in Multisensory Binding Can Predict the Varied Severity of Motion Sickness

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In neuroscience, research often focuses on the group, while ignoring large individual differences, which are left poorly understood.
One such example is the large individual variability in the susceptibility to motion-sickness (MS), the feeling of sickness during travel. Current explanations of MS focus on the sensory conflict, primarily between the vestibular and the visual systems. To account for the large individual differences in MS, we hypothesized that people feel MS only when the conflicting stimuli are perceived as bound together.
To test this hypothesis, we measured the persistence of multi-sensory binding in (1) audio-visual McGurk effect in which watching a moving mouth alters the auditory perception of phonemes (n=30); (2) The double-flash illusion in which two auditory beeps cause a single flash to be perceived as double (n=40), and (3) Visual-vestibular mismatch in which a cloud of moving dots interferes with a vestibular signal (n=40). In all paradigms, we varied the mismatch via temporal asynchrony (audio-visual) or heading direction (vestibular-visual) and computed a “binding-window” in which the binding persists.
To assess the severity of MS, we used two subjective symptom questionnaires. We found that (1) the temporal binding-window in the audio-visual experiments and (2) the heading binding-window in the vestibular-visual experiment, varied across individuals and were positively correlated (R>~0.7) with the MS questionnaire severity scores.
These results support our hypothesis and shed new light on the enigmatic differences between individuals regarding their susceptibility to motion-sickness. They also highlight the potential strength of studies focusing on individual differences and neurological diversity.

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Perceiving depth beyond sight: evaluating intrinsic and learned cues via a proof of concept sensory substitution method in the visually impaired and sighted

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This study explores spatial perception of depth by employing a novel proof of concept sensory substitution algorithm.
The algorithm taps into existing cognitive scaffolds such as language and cross modal correspondences by naming objects in the scene while representing their elevation and depth by manipulation of the auditory properties for each axis. The study, involving 40 participants, seven of which were blind (5) or visually impaired (2), investigates the intrinsicness of an ecologically inspired mapping of auditory cues for depth by comparing it to an interchanged condition where the mappings of the two axes are swapped.
All participants successfully learned to use the algorithm following a very brief period of training, with the blind and visually impaired participants showing similar levels of success for learning to use the algorithm as did their sighted counterparts. A significant difference was found at baseline between the two conditions, indicating the intuitiveness of the original ecologically inspired mapping. Despite this, participants were able to achieve similar success rates following the training in both conditions.
The findings indicate that both intrinsic and learned cues come into play with respect to depth perception. Moreover, they suggest that by employing perceptual learning, novel sensory mappings can be trained in adulthood. Regarding the blind and visually impaired, the results also support the convergence view, which claims that with training, their spatial abilities can converge with those of the sighted.

Finally, we discuss how the algorithm can open new avenues for accessibility technologies, virtual reality, and other practical applications.

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Topic 45

Sensory systems : Pain

THE NEURAL CORRELATES OF CENTRAL NEUROPATHIC PAIN IN INDIVIDUALS WITH SPINAL CORD INJURY

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Introduction: Central neuropathic pain (CNP) selectively affects individuals with SCI and has high comorbidity with psychiatric disorders. dorsolateral prefrontal cortex (dlPFC) and medial prefrontal cortex (mPFC) areas are involved in both pain psychiatric aspects. We examined wether disruption in normally observed negative dlPFC- mPFC resting state functional connectivity (RsFC) is associated with CNP and with psyciatric symptomatology.
Methods: A total of 36 post-SCI participants, 24 with CNP and 12 without, underwent RsFC scans and psychiatric questionnaires. DlPFC-mPFC RsFC levels ware compared, as well as prevalence of negative RsFC in each group. Finally, dlPFC-mPFC RsFC association with scores of psychiatric symptoms was calculated.
Results: Significant difference between groups was found in dlPFC-mPFC RsFC ($T(34)=-2.5955$, p-value= 0.01385). Negative dlPFC- mPFC RsFC was found predominantly in individuals without CNP compared to a predominantly positive RsFC in individuals with CNP ($Z= 13.89$, p-value < 0.0001). Furthermore, a positive correlation between dlPFC-mPFC RsFC levels and symptoms of depression ($r=0.39$, $P=0.029$) and PTSD ($r=0.35$, $P= 0.047$) was significant.

Conclusions: Negative dlPFC- mPFC RsFC, which characterizes the healthy population, is mostly absent among individuals with CNP, and is associated with symptoms of depression and PTSD. This suggests a possible target for intervention and personalized preventive treatment.

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Encoding of noxious stimulus in nociceptive terminals

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Nociceptive terminals detect and transmit information regarding noxious stimuli, thus initiating pain sensation. Since the terminals are inaccessible to electrodes, little is known about their electrophysiological properties. Here, we expressed the genetically encoded voltage indicator (GEVI) Archon1 in pain-sensitive neurons innervating the cornea. Using a high-speed microscope and holographic illumination we monitored the voltage dynamics in corneal nociceptive terminals in anesthetized mice in-vivo.

We discovered that both cold-sensitive and hot-sensitive terminals generate ongoing action potentials without the application of noxious stimuli. We also found that different terminals connected to the same axon showed unsynchronized firing, and only activity from one terminal propagated to the downstream axon. This result suggests non-linear signal integration involving complex filtering mechanisms.

Next, we co-expressed a channelrhodopsin together with Archon1, to allow simultaneous voltage imaging and optogenetic activation (Optopatch). We then recorded ongoing and evoked terminal activity in a model for inflammatory pain induced by inflammatory cytokines. Surprisingly, inflammation caused no change in the ongoing activity and resulted in reduced sensitivity to optogenetic stimulation.

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 differs from the CNS neurons.

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Topic 46

Sensory systems : Touch

An Attractor for Object Detection in Freely-Behaving Rats

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Objectives: We study perception as a closed-loop dynamical process. Percepts are hypothesized to take the form of attractors within a motor-sensory phase-plane. We analyzed object exploration via whiskers to characterize whether such attractors indeed emerge.

Methods: Freely-moving rats performed an object identification task. Whiskers were tracked in high-speed videos.

Results: During the rat's approach towards the object, contacts elicit a fast increase in whisker bending (base-curvature, a sensory variable), for relatively small changes in whisker position (base-angle, a motor variable). This characteristic motor-sensory relation is much less evident during free-air whisking. It is also more strongly associated with later contacts, compared to earlier ones. During contact, motor-sensory variables close to this relation are maintained for longer periods of time, compared to those farther away from it. The controlled coordination of whisker dynamics observed here was achieved despite variability in head-motion over trials.

Conclusions: Analyses revealed that the whiskers' dynamics converge towards a motor-sensory attractor over consecutive contacts, and tend to dwell more in its basin of attraction. This work proposes the first quantitative account of a naturally-occurring perceptual attractor in the tactile system, and in perception by freely moving animals in general.

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Topic 47

Sensory systems : Vision

TWO-PHASE EXTRA-RETINAL INPUT TO MONKEY'S V1: EFFECTS OF FIXATIONAL SACCADES ON POPULATION RESPONSES

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The eyes continually move and even during fixation they displace the retinal image across numerous foveal photoreceptors.
Fixational eye movements come in two primary flavors: slow ocular drifts that are interspersed with faster microsaccades (MSs).
Thus, stationary stimuli do not exist at the retina level, suggesting the existence of an extra-retinal input (ERI) in the visual cortex to correct for image motion and produce visual stability. We aimed to investigate the existence of an ERI in the primary visual cortex (V1) of behaving monkeys and used voltage-sensitive dye imaging to measure the neural population response, at high spatio-temporal resolution. The V1 population response aligned on MSs, revealed a two-phase modulation, in the absence of a visual stimulus: an early suppression transient followed by enhancement transient. Interestingly, the modulation spatial pattern varied, with enhancement primarily in foveal regions and suppression followed by delayed enhancement in parafoveal regions. The MS modulation in the absence of a visual stimulus was different from that evoked by an external motion of the fixation point, yet co-existed in the presence of a visual stimulus. Finally, increased neural synchronization was observed during the MS modulation. These results unravel an ERI that can be involved in visual stabilization.

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V1 NEURAL RESPONSE PRECEDES THE SACCADIC SHIFT OF VISUAL TARGET TOWARDS THE FOVEA

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Eye movements play pivotal role in active sensing of visual scenes, while saccades enable to move a desired region, to the fovea where the highest visual acuity is. Recent behavioral studies reported on stimulus feature-specific enhancements at the fovea, preceding saccades or microsaccades towards visual targets.
However, the underlying neurophysiological mechanisms are unknown. We investigated the neural mechanisms involved in visual information transfer between parafoveal and foveal regions to central fovea, relative to microsaccades. Using voltage-sensitive dye imaging we measured the spatio-temporal patterns of neural activity at high resolution, in the primary visual cortex (V1) of monkeys. The imaged V1 region encompassed a retinotopic map from the central fovea to parafoveal eccentricities.
This allowed analysis of the full extent of activation patterns triggered by a visual target transitioning from parafoveal to foveal regions, during pre-saccadic and post-saccadic periods. The target onset evoked an activation patch in V1, which, following a microsaccade to the target, shifted to the central fovea.
Interestingly, foveal neural activity began increasing before microsaccade onset, pre-empting the target landing at the central fovea. This effect, unobserved in fixation only or off-target microsaccades, could encode information transfer from parafoveal to foveal regions, supporting a mechanism for visual stabilization.

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Reading "GANDALF" from Macaque Primary Visual Cortex: modelling a topographic code for letters

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Predicting the neuronal response for visual images and reconstructing visual stimuli from neural activity are important key steps towards artificial vision. In this study, we aim to characterize the population responses in the primary visual cortex (V1) to contour letters and geometric shapes and develop a brain inspired model to predict these responses.
Our research refines an existing model by integrating two critical components: iso-orientation suppression (IOS) and end-stopped (ES) neural responses, which are critical for understanding V1 activity.
We used voltage-sensitive dye imaging (VSDI) to characterize the spatio-temporal patterns of V1 population response in behaving monkeys, to letters and geometric shapes. The VSDI method, ideal for investigating topographic maps, measures the population response with high spatial (meso-scale) and temporal (millisecond) resolution. Interestingly, V1 population responses exhibited increased neural activity at the shapes' corners and endpoints and a decreased population response along the linear edges. Using a non-linearity function for the IOS process, we show a significant improvement in the model's prediction accuracy and a good fit to the decreased responses along the linear edges.
The remaining gaps suggest the involvement of end-stopped neural responses that can better explain the enhanced responses at the endpoints of the letters and shapes.

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POPULATION RESPONSES IN V1 ENCODES STIMULUS VISIBILITY IN BACKWARD MASKING

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Visual backward masking (BM) is a powerful paradigm where a brief stimulus visibility is dramatically reduced when followed by a second stimulus, the mask. The stimulus visibility depends on the time interval between stimulus and mask onset (stimulus-to-mask onset asynchrony; SOA), when SOA becomes shorter, stimulus visibility decreases.
To date, the neuronal mechanisms underlying BM in the visual cortex are not well understood. To investigate this, two monkeys were trained on a texture discrimination task (TDT) and had to discriminate between vertical and horizontal targets embedded within a homogeneous patterned background. Using voltage-sensitive-dye imaging we measured population responses in V1 while the monkeys performed TDT with BM at variable SOAs. Behavioral performance was higher and reaction time (RT) shorter for longer SOAs.

Population response in the targets exhibited higher activity as compared to the background, a phenomenon known as figure-ground modulation (FG-m).
The amplitude of FG-m was strongly correlated with the monkey's behavioral performance. Error trials, where the monkey incorrectly reported the target, showed a reduced FG-m. An SVM classifier applied on the population responses revealed two temporal phases of target discrimination while showing maps of most informative pixels. These results reveal the neural mechanisms mediating stimulus visibility in V1.

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Causal Investigation of the Sources of Visual Perceptual Sensitivity Using Brain-Computer Interface

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The origin and significance of inter-trial variability in visual detection tasks is not fully understood and remains an object of debate in neuroscientific community. While some argue that it arises from neural background noise, others propose that it reflects functional subject-stimulus dynamics.
Resolving this issue requires establishing causal relationships between the different visual and neural processes. In this study, we present a novel experimental methodology to address this question. We conducted psycho-physical experiments while simultaneously recording subjects' electroencephalogram (EEG).
These EEG recordings were then utilized to train a predictive algorithm using machine learning techniques, such as quadratic discriminant analysis, and deep learning methods with task-specific preprocessing of real-time EEG data. The machine learning models achieved single-trial accuracy ranging from 65 to 93 percent. To modulate subjects' detection probability, we implemented a closed-loop PID control algorithm, based on each subject responses, which allowed us to achieve a successful clamping to a predefined value.
Our next step involves integrating these two key components, into a brain-computer interface (BCI) framework. This framework will allow to bypass subject feedback during experiments, clamp each of the processes involved in visual detection, and therefore hopefully provide valuable insights into the causal nature of visual inter-trial variability.

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Behavioral states control binocular vision through input-specific mechanisms

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Binocular vision is essential for depth perception and goal-directed behaviours such as navigation and prey hunting - however, under certain behavioural conditions, reduced binocular and enhanced monocular (i.e. peripheral) vision might serve an animal's behavioural demands better.
Whether binocular vision undergoes behavioural state-dependent changes is not known, yet classic studies indicate that binocularity in the adult visual cortex is fixed. By combining multi-modal behavioural tracking and calcium imaging in excitatory neurons in the binocular zone of the primary visual cortex of adult mice, we find that (1) the binocularity of single neurons and binocular vision are not fixed but rather change rapidly according to an animal's arousal state, and (2) these state-dependent changes are driven by input-specific enhancements of sensory responses rather than by state-dependent changes in eye position or pupil dilation.
Thus, since inputs to neurons in the visual cortex monocular zone are strengthened at high arousal, these findings indicate that the relative impact of binocular vision from the centre of the animal's visual field decreases at high arousal while the impact of peripheral monocular vision increases which, in turn, adapts an animal's visual perception to its behavioural demands e.g. to better perceive an approaching danger.

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Characterizing the Role and Projections of GABAergic Retinal Ganglion Cells in Visual Processing

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Retinal ganglion cells (RGCs) are conventionally known for transmitting visual information through the excitatory neurotransmitter glutamate.
However, a distinct set of GABAergic RGCs, which release the inhibitory neurotransmitter gamma-aminobutyric acid (GABA), has been found in various species. In mice, these GABAergic RGCs project to key retinorecipient regions such as the suprachiasmatic nucleus (SCN), olivary pretectal nucleus (OPN), lateral geniculate nucleus (LGN), and superior colliculus (SC).
While GABAergic RGCs projecting to the SCN, OPN and SC were shown to regulate circadian rhythms,pupillary light reflex, and contribute to looming-evoked defensive behavior, respectively, role and identity of dLGN projecting cells remain unknown. To explore these RGCs, we used GAD-Cre mice with intraocular injections of flexed EGFP to map their projections in the brain.
As expected, EGFP signals were detected in the SCN, OPN, SC, and the LGN. Interestingly, we observed projections in both the ipsilateral and contralateral LGN. Two-photon targeted patch-clamp recording and calcium imaging of retinas injected with flexed GCaMP will allow us to characterize the structure and function of these GABAergic RGCs.
The findings will enhance our understanding of these unique RGCs and lay the groundwork for studying their roles in both image-forming and non-image-forming visual pathways.

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INHIBITION OF PROTEASE ACTIVATED RECEPTOR 1 AS A NOVEL TREATMENT FOR DIABETIC RETINOPATY

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Thrombin and its cellular protease-activated receptor-1 (PAR1) play a role in diabetes neurological manifestations and are expressed in the ocular microenvironment of diabetic retinopathy (DR) patients.
We studied the involvement of this pathway in a DR mouse model. Diabetes was induced in C57BL/6J mice by streptozotocin. Diabetic mice were treated with the PAR1 modulator PARIN5 by IP injections (375 ng/kg) and eye drops (100nM). Retinal function was assessed by Electroretinogram.
Thrombin activity was measured in the neuroretina and PAR1 expression was determined by immunofluorescence analysis and western blot. The mRNA expression of PAR1/thrombin pathway components was determined by qRT-PCR.
Increased PAR1 staining was observed in the nuclei of photoreceptors, bipolar and ganglion cells in DR mouse neuroretina compared to PARIN5-treated and non-diabetic mice. Increased PAR1 ($p=0.039$), and decreased FXa and prothrombin mRNA were found in the neuroretina of diabetic mice compared to non-diabetic ($p=0.007$) and treated mice ($p=0.181$, $p=0.150$). PARIN5 treatment prevented the reduced ERG b/a wave ratio in diabetic mice ($p=0.004$) DR is associated with an increase in the expression of PAR1/Thrombin pathway in the mouse neuroretina.
PARIN5 treatment prevented the diabetes-induced damage to retinal function, suggesting that targeting this pathway may present a new strategy for DR treatment.

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Retina resuscitation following Prolonged Ischemia

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Retinal neurons lose their functionality rapidly following death or prolonged ischemia, however, recent publications reported that light signaling in the retina can be revived following prolonged ischemic periods. Here we extensively dissect the several aspects of retinal cells function following prolonged ischemia and resuscitation not previously reported on.
The retina of WT rats was subjected to varying ischemia times (0 to 240min) under two different ambient temperatures after which it was mounted on a Multi-Electrode-Array containing oxygenated Ringer's solution. The effect of ischemia on several response features were investigated. Retinal function gradually degraded with increasing ischemic time, as was inferred from the decrease in the number of responding RGCs and RGCs' firing rate (3 fold) ; the ON-response ERG amplitude gradually decreased with increasing ischemia time (up to 2-fold) whereas the OFF response decreased to a lesser extent.
Moreover, depending on tissue temperature, retinal function can be partially rescued by re-oxygenation even following a long ischemic time of up to 240min. A robust in-vitro model for the tissue-level and single cell investigation of various interventions aimed at neural tissue preservation following ischemia, was introduced, offering hope for the resuscitation of retinal or other neural tissue after prolonged ischemia times.

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Fundamental Features of Vision in Single Cells under Prosthetic and Natural conditions

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advancements in retinal prostheses for vision restoration in patients with Age-related Macular Degeneration (AMD), raises the need to address the question of the processing of combined natural and prosthetic vision.
Here we present our efforts towards understanding this issue at the single-cell level. We performed extracellular recordings in WT rats subretinally implanted with a photovoltaic device fabricated by our collaborators at Stanford University. Prosthetic (910nm) and natural (525nm) stimulations were performed using a customized projection system, enabling the stimulation of the photovoltaic implant or the healthy retina.
We investigated the intensity tuning of single cells under both conditions using short light pulses (2,4,10msec) with varying intensities between 4-600nW/mm2 and 1-3000µW/mm2 for natural and prosthetic stimulation respectively. In addition, the Critical Flicker Fusion (CFF) between 1-64Hz was also explored under both stimulation conditions.
Both prosthetic and natural vision intensity tuning of single demonstrated a response dynamic range of approximately 1 order of magnitude. CFF investigations revealed the phase locking of single cells up to 4Hz, while higher frequencies induced an ON/OFF-like response under both conditions. This work provides valuable insights into the processing of combined prosthetic and natural vision, a key issue in AMD patients implanted with photovoltaic devices.

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Contrast sensitivity in adults with ADHD

Hani Tsruya, Maria Lev, Uri Polat

Contrast sensitivity (CS) is an important visual function typically measured as a function of spatial frequencies.
It provides a comprehensive analysis of visual performance and allows estimation of the minimum threshold required to detect real-world objects at various spatial frequencies. As a low-level visual function, CS significantly impacts overall visual perception.
Previously, we showed that performance of adults with ADHD is significantly worse than the control group in a crowding task. In this study, we aimed to explore whether ADHD also affects CS. A total of 27 participants (17 control, 10 ADHD) underwent testing of their CS. The task involved presenting single target stimuli (Gabor patches) of 4, 6, 9 and 12 cycles/degree (CPD) for 40 and 80 ms. Results revealed a significant difference in CS between ADHD and control groups, particularly at higher spatial frequencies.
We suggest that reduced CS in ADHD may impact visual performance in everyday tasks.

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Investigating the modulation of visual crowding by visual category

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Visual crowding, the difficulty in recognizing objects amidst clutter, is often attributed to general limitations of the visual system and therefore is assumed to affect all visual categories similarly.
However, considering the diverse neural mechanisms supporting different visual categories and their different visual field sensitivities, we hypothesized that crowding might vary across categories. To test this, here a group of participants underwent a series of crowding experiments, each with stimuli from different visual categories (faces, houses and letters).
Stimuli were presented in crowded (flankers from the same category as the target) or uncrowded conditions at central or peripheral (6 deg. right/left of fixation) locations with peripheral stimuli enlarged to overcome the central magnification factor. Stimuli were presented for 150 ms and eye movements were monitored to ensure data of peripheral conditions reflected peripheral vision performance.
As expected, performance (accuracy and reaction times) was similar for central and uncrowded peripheral conditions for all categories. Under crowded conditions peripheral performance declined in a comparable manner for all categories.
Additional analyses examined within and across category associations related to crowding.
These results suggest that crowding affects multiple categories including those associated with central-vision and those associated with peripheral-vision.

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Support for the valence-specific hypothesis in parafoveal perception of facial emotional expression across two studies

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There is no consensus about the brain mechanisms behind facial emotion perception. Two leading theories, the Right-Hemisphere Hypothesis (RHH) and the Valence-Specific Hypothesis (VSH) disagree on the neural mechanisms supporting positive valence (pleasant) facial emotions.
The RHH advocates right hemisphere dominance and VSH advocates left hemisphere dominance. The divided visual field (DVF) paradigm utilizes the human visual system architecture to reveal potential hemispheric specialization by presenting stimuli unilaterally.
Here in two separate studies (with KDEF (n1=37) and NimStim |(n2=37) stimuli) we relied on the DVF paradigm to assess the contribution of right and left hemisphere to valence perception of faces with positive, negative or neutral expressions (briefly (200ms) presented in different visual field locations (up to 4° while eye movements were monitored)).
Across the two studies we found (i) right-left visual field modulations at 4° but not at 2°, (ii) support for the VSH but not for the RHH (higher positive valence accuracy for right- relative to left- visual field presentation), and (iii) right-left visual field within-valence correlations.
Our results provide consistent support for the VSH for parafoveal facial stimuli beyond 2°. They also indicate that the mechanisms supporting specific valence perception at different visual field locations are associated.

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TOPOGRAPHIC ORGANIZATION OF DIRECTION- AND ORIENTATION-SELECTIVE RESPONSES IN THE MOUSE VISUAL THALAMUS

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The lateral geniculate nucleus (LGN) of the thalamus is a major retinal target, involved with processing and relaying visual information including direction selectivity (DS) and orientation selectivity (OS).

Yet, how DS and OS are organized in the LGN is poorly understood, as well as the extent to which this information is inherited from the retina or generated de novo in the LGN.

To address this, we performed extracellular in vivo recordings using high-density electrode arrays that spanned the LGN of mice and studied DS and OS responses with and without DS retinal inputs. Our survey revealed two distinct patterns of organization: LGN DS responses are absent in the central visual field, and are topographically aligned to optic flow dynamics of forward self-motion around the central visual field, whereas OS responses are found throughout the entire visual field.

Using transgenic mice in which retinal DS was eliminated, we found that DS- but not OS-LGN responses were dependent on retinal DS. Our results show that LGN DS responses are inherited from the retina, but also suggest that retinogeniculate transfer may be nonuniform and dependent on topography, optimizing representations that support visually-guided behaviors.

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Exploring the Alignment of Optic Flow and Direction-Selective Cells in the Mouse Visual Thalamus

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Optic flow, the patterns of apparent motion in the visual field generated by self motion in an environment, is a fundamental aspect of visual perception, crucial for navigation and spatial orientation.
Previous research by Sabbah et al., has shown that preferred directions of direction-selective (DS) ganglion cells in the retina align with optic flow patterns experienced by the mouse during forward motion. In addition, recent work from our lab suggests a similar alignment of DS cells in the lateral geniculate nucleus (LGN), a major retinal target.
Expanding on these findings, our study explores the relationship between DS cells in the mouse LGN, particularly in optic flow. By examining the interactions between optic flow and DS cell activity across different visual and self-motion conditions, we aim to uncover how these cells contribute to the processing of dynamic visual information, i.e. optic flow.
Our research considers both naturalistic and controlled environments, with an emphasis on understanding how DS cells align to various visual stimuli and different contexts.
This study aims to deepen our understanding of how the mouse visual system processes optic flow and how DS cells may contribute to this process under different self-motion and visual conditions.

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Topic 48

Sleep

Expectation and surprise in the sleeping brain: Auditory omission prediction error response in NREM

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Sleep is a reversible condition of reduced awareness and responsiveness to the external environment.
Nevertheless, even during sleep, organisms must regularly sample the environment, create predictions, and detects their violation. Indeed, compelling evidence indicates that the sleeping brain can detect simple sensory deviation. However, only a few studies investigated more complex predictions, and it remains unclear how sleep modulates the formation of predictions and surprise responses. To answer this question, we recorded high-density EEG from 28 healthy participants in sleep and wakefulness while they passively heard an auditory oddball-omission paradigm.
The paradigm included expected and unexpected omitted sounds with intermediate complexity rules, which enabled to disentangle between the neural response to the "pure" prediction error and the neural response to the stimulus's physical properties.
ERP analysis showed a significantly increased negativity at 100-300ms following omission onset in the unexpected omission condition compared to the expected omission in wakefulness, N2 and, REM sleep, but not in N3.
This result implies that the sleeping brain is able to create predictions more complex than a mere sensory deviation and that this ability is compromised in slow-wave sleep.

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Distinct locus coeruleus efferent pathways promote arousal

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The locus coeruleus (LC) is the main source of norepinephrine (NE) to the forebrain, and is involved in multiple functions including arousal and vigilance state regulation. However, the extent to which LC-NE modulation operates heterogeneously to differentially modulate arousal in target regions remains unknown. We investigated this in mice by examining anatomical, physiological, and functional modularity of LC-NE neuromodulation across the forebrain and brainstem. First, via anatomical investigation with retrobeads and retro-AAV viruses we found that LC neurons projecting to forebrain and brainstem are anatomically distinct, and that forebrain-projecting neurons are located more dorsally.
Next, we monitored extracellular NE levels with GRABNE, confirming its effectiveness with optogenetic activation and by observing lower NE signaling in REM sleep and around sleep spindles. GRABNE dynamics recorded simultaneously in forebrain and brainstem revealed distinct sound-evoked activation patterns during sleep, attesting to modular LC-NE neuromodulation. Finally, we used optogenetic manipulation to either activate LC subpopulations (retro ChR) or selectively silence synapses in the projection target (PdCO) and find that the LC->brainstem pathway has a privileged role in eliciting arousal and sound evoked awakening compared to the LC->forebrain pathway.
Our results show modular anatomical and physiological organization within a system that was traditionally thought of as homogeneous.

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Sensory Disconnection during Sleep: Insights from Neuropixels recordings in Naturally Sleeping Mice

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Sleep is a fundamental physiological state that involves altered sensory processing. Neuronal responses along the cortical auditory hierarchy, especially late response components, reveal differences between wakefulness and sleep. In humans, alpha-beta desynchronization (ABD, stimulus-induced reductions in 10-30Hz power of field potentials) are prevalent in wakefulness but disrupted in sleep.
ABD changes suggest a disruption of feedback signaling during sleep, but direct evidence is lacking. Our goal is to investigate cortical information flow of auditory responses during sleep and wake. We performed chronic electrophysiology with neuropixels electrodes in freely moving mice, combined with auditory stimulation, and sleep monitoring with polysomnography and video.
A novel 3D-printed probe enclosure enabled long-term chronic monitoring of spiking activity and LFPs along the mouse temporal lobe including core auditory cortex (A1) as well as dorsal auditory cortex and temporal association area. Localization is facilitated by Dil probe staining and histology. We are successfully monitoring auditory responses, with early auditory cortex showing earliest (<15ms) and strongest responses, whereas high-order regions show delayed and sparser responses. In some cases, we can observe ABD responses as reported in human intracranial studies, now allowing to study in mechanistic detail their relation to feedforward and feedback aspects of information flow.

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Claustrum projections to anterior cingulate cortex are associated with deeper disconnected sleep

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Objectives: Sleep is characterized by low levels of engagement. The claustrum, particularly its reciprocal connections with executive regions in the frontal cortex, has been linked to attention and sleep.
Our aim was to characterize how the activity of a specific subpopulation of claustrum neurons projecting to the anterior cingulate cortex (ACCp) may be involved in sleep depth, linked to slow-wave activity (SWA) and the likelihood of waking up in response to auditory stimuli.
Methods: We conducted simultaneous recordings of EEG and fiber photometry in claustrum over a 12-hour period to examine the correlative association between changes in calcium dynamics and vigilance states. A separate experiment tested for causal connection by activating the ACCp projection using excitatory DREADD hM3Dq chemogenetics. Sleep was monitored with EEG/EMG and video while we assessed how CNO/saline injections affect sleep architecture, SWA, and sound-evoked awakening.
Results and Conclusions: Our findings indicate that claustrum neurons projecting to the cingulate cortex are maximally active during deep unresponsive slow-wave sleep, when DREADD mice under CNO influence rarely wake up in response to sensory stimuli, supporting an association between claustral ACC-p activity and disconnection from the environment.

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Non-invasive detection of interictal epileptiform discharges in the mesial temporal lobe during sleep

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Interictal epileptiform discharges (IEDs) are brief paroxysmal electrographic events observed between seizures in epilepsy patients, and their occurrence during sleep may impair memory consolidation.
We hypothesized that some IEDs occurring in the medial temporal lobe (MTL) can be detected non-invasively using machine learning (ML) tools. First, in epilepsy patients implanted with depth electrodes, neurologists manually tagged some IEDs in MTL intracranial data, and a ML model successfully extended these annotations to full-night data. Second, following preprocessing and feature extraction, a model was trained to use EEG data from select electrodes to detect simultaneously-recorded MTL IEDs, and could successfully identify ~2-5% of such events with >75% precision. We are currently investigating whether IEDs detected non-invasively may be associated with specific features such as typical amplitude, duration, or spatial spread profiles, and validating our detection with separate datasets. Our work establishes that MTL IEDs can be identified noninvasively, opening new diagnostic avenues in several neurological conditions associated with IEDs including epilepsy, Alzheimer's and other neurodegenerative diseases, ADHD, Autism, and following traumatic brain injury (TBI). Funding: Supported by the European Research Council (ERC-2019-CoG 864353).

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Memory generalization and overgeneralization in sleep

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Overgeneralization and sleep disruption are major components of anxiety and post-traumatic stress disorder (PTSD).
This study explores the potential links between these elements. We designed a paradigm where participants learned to associate three faces with positive, negative, or neutral outcomes. We evaluated their generalization of these faces by examining responses to morphed faces created by blending the three original faces in different proportions. We assessed immediate generalization after the faces were associated with the valence and late generalization after daytime consolidation or full-night sleep. Our findings suggest that sleep shifts generalization toward positive stimuli: After sleep, participants tended to generalize the positively associated face, while following the wake period, participants tended to generalize the negatively associated face. In another experiment, fMRI data revealed that higher amygdala activity during learning predicted immediate generalization of the negative face, followed by restoration and generalization of the positive face after sleep.
Similar patterns were observed in other limbic regions. This activity did not correlate with generalization during wake consolidation. High-density EEG recordings indicated that sleep spindle power correlated with positive face generalization and the transition from negative to positive generalization after sleep. These results emphasize the role of sleep in modulating generalization, specifically in reducing negative and enhancing positive stimuli generalization. This research advances our understanding and potentially informs therapeutic strategies for anxiety and PTSD.

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SWIR imaging for touchless pupillometry and gaze estimation in closed eye conditions

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Objective: Arousal changes dynamically during sleep and sleep-related states, and such changes may be captured by pupil dynamics. However, pupillometry is typically intermittent, qualitative, manual, and limited to open-eye situations. Methods: Here, we combine short-wave infrared (SWIR, ~ 0.9-1.7 μm) imaging with dedicated image processing algorithms to monitor pupil size and gaze direction in closed eyes. Two experiments (N=43) included (1) induction of a stimulus-evoked pupillary light reflex (PLR, to validate pupil size monitoring), and (2) directing eye movements towards screen targets (to validate gaze direction monitoring).

Data analysis was performed with a custom approach quantifying changes in brightness around the pupil area or with a deep learning U-NET-based procedure. Results: Analysis of SWIR data in closed eyes and its comparison to open eyes conditions successfully identifies PLR events in single trials and in nearly all (93%) individuals, as well as estimating gaze direction with ~10 degrees of visual angle. Conclusion: Ongoing work is now further improving the optical setup and enabling pupillometry in the face of eye movements. Our approach is contactless and can potentially measure pupil size and gaze direction continuously for hours.

This technology has many clinical and research applications such as monitoring arousal during anesthesia, sleep, and in unconscious patients.

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Sleep and fall risk in Parkinson's disease

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Objectives: To evaluate the association between sleep and fall risk in Parkinson's disease (PD) patients, and to explore whether this relationship is mediated by motor and cognitive functions.

Methods: PD patients underwent polysomnography, clinical assessments, cognitive evaluations, and gait analysis. Patients were categorized as fallers and non-fallers based on reported falls in the past year.

Results: A final cohort included 33 fallers and 71 non-fallers. Fallers exhibited poorer gait and cognitive performance, lower sleep efficiency (SE: 62.3±18.0% vs. 71.8±15.6%, $p<0.01$), and shorter sleep time compared to non-fallers. Poor sleepers (SE<50%) had a higher faller proportion (59%) versus good sleepers (26%, $p<0.01$). Lower SE was associated with poorer gait and cognitive performance. The effect of SE on falls was fully mediated by daily living activity (MDS-UPDRS II) score and was partially mediated by gait speed during dual-task walking (trend significant at 90% CI).

Conclusions: Fallers demonstrate worse sleep metrics, with poor sleep associated with a higher fall risk. Sleep may impact daily living activities, potentially reducing mobility and increasing fall risk. Poor sleep may reduce cognition and motor function, further elevating fall risk. Improving sleep could potentially reduce fall risk in PD patients.

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EFFECTS OF SLEEP DEPRIVATION ON TIME PERCEPTION AMONG MEDICAL RESIDENTS: A PILOT STUDY

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Objective: This study aimed to explore the impact of sleep deprivation on time perception among medical residents that perform long shifts.

Methods: Nine medical residents participated in a computer-based prospective time reproduction task. Participants were presented with 30 trials of a dot appearing for 500-3000 milliseconds (randomly). After the dot disappeared, they pressed the space bar to indicate their perceived duration of the dot's appearance. The task was conducted at the start, after 13 hours, after 19 hours, and at the end of a 26-hour shift. Additionally, the task was repeated the following day after rest. The primary outcome measure was the total reproduction durations for each assessment. A repeated-measures ANOVA compared this measure across the different time points.

Results: No significant within-subject effects were found. However, when examining the durations by categorizing them into short (<1500 ms) and long (≥1500 ms), a significant over-estimation effect emerged throughout the shift for the short duration stimuli (p=.003, e.g., 166 milliseconds difference on average between start and end of 26-hour shift). These findings suggest a potential decrease in attentional resources allocated to time perception tasks.

Conclusion: Sleep deprivation may adversely affect time perception, but more participants are required to validate these findings.

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Establishing a CRISPR/Cas9-mediated system for the induction of a tissue and time specific DNA damage

Michal Zarfati, Gali Krayden, David Zada, Adir Monsonego, and Lior Appelbaum

Sleep is a fundamental process which affects many physiological functions across species, including neuronal plasticity, memory consolidation, metabolic regulation, and DNA repair.
Despite its significance, the molecular mechanisms underlying sleep homeostasis and its single-cell-level manifestations remain unknown. Utilizing zebrafish, a transparent vertebrate model with a conserved genome and a central nervous system like mammals, we found that DNA damage accumulates in the dorsal pallium neurons during periods of vast neuronal activity such as wakefulness with subsequent efficient repair during sleep, a process mediated by the DNA damage detector Parp1, which links homeostatic pressure to sleep promotion. However, existing methods for studying the relationship between neuronal activity, DNA damage, repair and sleep have limitations.
Here, we established a CRISPR/Cas9 system that allows the induction of tissue-specific DNA damage while avoiding gene mutations. Our findings show that targeted DNA damage induction in neurons increases homeostatic pressure and promotes sleep.
Furthermore, by integrating the bi-partite complex Cre/loxP with CRISPR/Cas9 and Gal4/UAS systems, we report on the creation of a plasmid system that will allow temporal and spatial control over the induction of DNA damage, considering developmental stages and cellular tissues.

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Home-based olfactory biofeedback for implicit learning to reduce sleep bruxism

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The potential for sleep-based learning, particularly in implicit information acquisition, has long intrigued researchers. A promising technique for reinforcing unconscious behaviors is biofeedback during sleep.
We investigated sleep learning through olfactory biofeedback, which supports learning with minimal sleep disturbance due to its unique neural pathway. Our study focused on sleep bruxism, a movement disorder characterized by repetitive jaw muscle activity. We used automatic delivery of unpleasant olfactory feedback immediately following each bruxism event during sleep.
We developed software for participants to conduct experiments at home, enabling long-term, naturalistic data collection. Data from 19 participants was analyzed: 10 in the experiment group, who received unpleasant odor feedback, and 9 in the control group, who received clean air.
Nine nights of sleep were recorded for each participant: an adaptation night, three baseline nights, two feedback nights, and three post-feedback nights. We trained a convolutional neural network for offline bruxism detection to quantify bruxism each night. Preliminary results show a significant reduction in bruxism for the experimental group ($p=0.0064$), with 7 out of 10 participants improving, compared to only 2 out of 9 in the control group. This approach presents a promising proof of concept, advancing our understanding of sleep-based learning mechanisms.

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Topic 49

Translational neuroscience

Recreating the epileptic aura with generative AI

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Individuals suffering from epilepsy often experience a preceding sensation immediately prior to the epileptic seizure. This sensation is termed the 'epileptic aura' and, depending on the location of the epileptic focus, can take the form of a visual, auditory or even an emotional experience. In the current study, we worked with a patient with implanted intracranial electrodes (stereo EEG) who frequently experienced very typical visual auras. We tested whether we can artificially recreate the patient's auric experience using generative AI tools, and whether such aura-like stimulus would uniquely affect his neural activity. The experimental session included several parts – voluntary visual imagery of the aura, recollection and narration of the aura, and viewing of AI-generated videos meant to recreate the specific patient's aura. We found that the AI-generated auric video triggered a full-blown epileptic seizure spanning from the hippocampus to the occipital cortex. Viewing of control videos, that were rated by the patient as being less similar to his auric experience, did not trigger such epileptic activity. Similarly, recollection of his auric experience also caused the patient to have epileptic activity. This unique novel tool enables us to investigate the connection between specific patterns of sensory processing and epileptic activity.

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Bicistronic constructs for all-optical interrogation of neuronal circuits using two-photon optogenetics

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The integration of two-photon optogenetics with two-photon imaging marks a significant advancement in neuroscience, offering unparalleled capabilities to manipulate and observe neuronal activity. This approach enables imaging of large neuronal populations in vivo, and access to neural ensembles governing complex behaviours and cognitive functions. Key to this methodology is the precise co-expression of opsins and sensors within specific neurons, allowing for both optical control of neurons and readout of neural activity. Previous iterations of two-photon optogenetics predominantly relied on opsins that were either relatively slower or more sensitive to blue light, which although effectively induced spiking, were plagued by the issue of optical 'crosstalk'. Crosstalk occurs when the imaging laser inadvertently activates the opsin during imaging, potentially confounding results. Furthermore, previous iterations often required co-expression of the actuator and sensor via two different AAV vectors, which usually led to inefficient and non-stoichiometric co-expression. To overcome both of these shortcomings, we developed a novel set of bicistronic constructs co-expressing the fast-acting red-shifted channelrhodopsin vfChrimson alongside with jGCaMP8s/m. In these constructs, both the opsin and sensor were specifically soma-targeted to reduce crosstalk, decrease the background during calcium imaging, and increase somatic photocurrents. We validated these constructs by quantifying the evoked photocurrents through single-photon stimulation in neuronal cultures and subsequent testing in mouse cortical neurons using AAV vectors and two photon holographic photostimulation. The multiple variants we constructed balance imaging and stimulation effectiveness, enabling all-optical experiments with optimal co-expression and minimal crosstalk.These bicistronic soma-targeted constructs thus represent a significant enhancement for two-photon experiments, providing precise control over neuronal activity while mitigating the unwanted effects of optical crosstalk.

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The Synergistic Effect of SIXAC and Chemotherapy as a Potential Therapy for Glioblastoma

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Glioblastoma (GBM) is the most common and aggressive primary brain tumor. Thrombin, a coagulation factor, plays a significant role in GBM pathogenesis through its activation of Protease Activated Receptors (PARs) and enhancement of nerve growth factors in glial cells. PAR-1, the primary thrombin receptor expressed in the brain, is upregulated in GBM and its inhibition is proposed as a potential treatment. In this study, we used a PAR-1 inhibitor named SIXAC in combination with standard chemotherapy. SIXAC, designed based on the thrombin binding-site sequence of PAR-1, was tested with Temozolomide (TMZ), a standard GBM treatment. The proliferation rate was assessed in CNS-1 glioma rat cells by Incucyte Live-Cell Analysis System. GBM model rats were treated using an Alzet pump and assessed for survival. SIXAC alone did not show a significant effect on CNS-1 cells. However, when SIXAC was combined with TMZ, a significant decrease in proliferation was measured, compared to control, SIXAC, or TMZ-only treatment ($p<0.05$). GBM model rats, that were treated with the SIXAC-TMZ combination, presented significantly prolonged survival, compared to SIXAC-only treatment ($p=0.02$). In conclusion, SIXAC may have the potential as an add-on therapy to increase the efficacy of conventional therapy for GBM treatment.

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TRANSCRIPTIONAL REGULATION DEMONSTRATING A CONSTITUTIVE PERSONALITY TRAIT CAPTURED IN MICE MODELS

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This study explores the relationship between personality and epigenetics, specifically how transcriptional regulation influences these traits. Using a 'social box' setup, we studied mice in semi-enriched environments, tracking their individual and social behaviors automatically. We identified "identity domains" (IDs), representing stable personality traits with varying inter-individual and consistent intra-individual characteristics. Four unique IDs were found, correlating with distinct behaviors across social contexts. We aimed to uncover the transcriptional signature for each ID by analyzing RNA-seq data from three brain regions (INS, mPFC, and BLA) and identify gene clusters strongly associated with each ID. Preliminary qPCR validation showed significant correlations between specific IDs and gene expression clusters. In the subsequent phase, we will explore the epigenetic regulation of unique gene expression per ID. By shedding light on emotionally driven behaviors and fundamental aspects of personality, this research enhances our understanding of biologically significant and evolutionarily relevant meta-behavioral phenotypes. It contributes valuable insights into the complex interplay between brain-specific mechanisms, gene expression, and stable personality traits, potentially paving the way for new avenues of research in neuroscience and psychology.

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DELAYED CONTRAST MRI FOR DEPICTING SHORT/LONG TERM SUBTLE BBB DISRUPTION IN TRAUMATIC BRAIN INJURY

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Introduction Short term BBB disruption (BBBd) is known to play a vital role in cognitive decline/dementia after traumatic brain injury (TBI). Here we applied delayed-contrast MRI (DCM) to detect/quantify long-term, subtle BBBd in mice following moderate TBI. Methods 57 mice with TBI were followed by DCM up to 540 days post-injury, following which brains were extracted for histological validation. Results Significant BBBd was observed at the injury site in all TBI mice. DCM revealed BBBd volumes x2.5 larger than T1-Gd enhancing volumes until day 133, when T1-Gd showed no further enhancement. BBBd volumes at the injury site decreased sharply (x3.666±0.004) by day 30, and BBBd intensities dropped from 20.6±1.5% to 10.4±1.5%, remaining constant up to day 540. Significant correlation ($r2=0.78;p<0.02$) was found between DCM-BBBd and histological BBBd biomarkers. Significant BBBd (4.8±1.0%) was found in the contralateral posterior cortex until day 540. Ipsilateral ventricle volume significantly increased up to day 30 (x5.455±0.001 of aging controls) and further by x1.429±0.001 by day 540 with significant blood-CSF barrier disruption. Conclusions DCM enabled depiction/quantification of long-term BBBd at the injury site, ventricles, and distant cortex regions. These findings point to chronic BBBd as a key player in the mechanisms leading to dementia following TBI.

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Non-coding RNA changes in adolescent stress-exposed female rats and their offspring

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Objectives: Pre-reproductive stress (PRS) affects behavior and the expression of mRNA and microRNA (miRNA) in adolescent female rats and their offspring. This study examines whether chronic unpredictable stress (CUS) impacts transfer RNAs (tRNAs) and their fragments (tRFs) in the prefrontal cortex (PFC) and blood of female rats and their offspring, explores tRNA/tRF/miRNA expression in the female germline, and investigates corticosterone (CORT) exposure in oocytes. Methods: Adolescent female rats underwent CUS for 7-days. PFC, blood, and oocytes were collected at 4-and 14-days post-stress, and from neonate offspring. Levels of tRNAs, tRFs, and miRNAs were measured using YAMAT-seq, sncRNA-seq, and RT-PCR. Oocytes were treated with CORT to assess miRNA/Crhr1 expression post-exposure. Results: Significant differences in tRNA isodecoders and tRFs levels were observed in the PFC at both time-points. tRFs and miRNAs were detected in oocytes, but their levels were mostly unaltered by stress. PRS did not impact isodecoders levels but altered tRF expression in offspring. CORT-exposure increased miRNA levels and decreased Crhr1 expression in oocytes. Conclusions: Stress influences miRNA/tRNA/tRF expression in the brain, and sncRNA changes in blood and oocytes may contribute to the intergenerational transfer of stress effects. CORT's impact on miRNA/Crhr1 expression further supports sncRNAs' role in stress mediation.

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MOLECULAR MECHANISMS UNDERLYING THERAPEUTIC ACTION OF TRANSCRANIAL DIRECT CURRENT STIMULATION

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Transcranial direct current stimulation (tDCS) is a non-invasive neuromodulatory technique that transiently alters neuronal activity by application of sub-threshold current. Despite its growing popularity, its mechanism of action is not well understood. Results of nuclear magnetic resonance (NMR) studies in humans suggested that tDCS causes metabolic changes in the brain. We aimed to confirm whether tDCS induces such metabolic alterations and to delineate the affected pathways. For this, we performed tDCS or sham in rats. Following, we extracted the targeted cortical brain tissue and performed metabolomics workup using LC-MS/MS. In addition, we analyzed publicly available transcriptomic dataset of tDCS, to determine the differential gene expression in light of the metabolomics data. Later on, we performed another tDCS study in mice, where mice went through a battery of behavioral tests, followed by brain tissue sampling for 1H-NMR metabolomics. Altogether, we observed changes in metabolites that relate to mitochondrial functioning and glycolysis. These results coincided with the transcriptomics analyses that also showed altered glycolysis and mitochondrial function. Interestingly, we also observed an alteration of calcium-related pathways. Taken together, our results uncover the metabolic effects of tDCS, suggesting that tDCS affects calcium dynamics leading to metabolic alterations, mostly modulation of cellular bioenergetic-related metabolism.

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Topic 50

Social models and mechanisms

Nucleus Accumbens Dynamics during Social Fear Conditioning: Impact of Acute Social Isolation

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With the surge in social isolation events during the COVID-19 pandemic, understanding its impact on mental health has become crucial. Acute social isolation has been shown to impair cognitive functions and alter social recognition memory in animal models. Social conduct, mental well-being, and productivity all get seriously compromised by both social fear and social isolation stress. Despite significant research, the exact behavioral and neural mechanisms behind social fear are unknown. Emerging evidence highlights the key role of the nucleus accumbens (NAc) in social behavior, yet its contribution to social fear memory and its sensitivity to acute isolation remain elusive. Here, we used a paradigm of social fear conditioning (SFC), where adult male C57BL/6J mouse received electric shocks upon interacting with a CS+ but not with a CS- conspecific. The protocol involved baseline tests, followed by SFC and recall assessments at 30 minutes and 24 hours post-conditioning. Using in vivo fiber photometry, we recorded NAc activity in adult mice during baseline and recall sessions. Group-housed mice showed a significant increase in NAc activity during recall sessions, specifically when interacting with the CS+ conspecific, compared to baseline. In contrast, isolated mice did not show increased NAc response following SFC. These findings suggest that the NAc is involved in the acquisition of social fear memory and that this involvement is impaired under acute social isolation.

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Searching for a Dedicated Social Cognition Network

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Social cognition, a multifaceted process encompassing various social skills, is a subject of intensive study in neuroscience. Whether it constitutes a unified process with distinct facets or operates through separate mechanisms tailored to specific contexts is debated. Moreover, the extent to which social cognition diverges from general cognition remains unclear. To address these questions, we devised tasks featuring social and non-social versions conducted within and outside fMRI settings. Tasks ranged from movie viewing to emotion categorization, motion prediction, working memory, and attention. Our findings revealed a consensus among participants toward a common "ground truth," yet substantial individual variability persisted as a stable trait. Interestingly, this variability differed notably between the social and non-social task variants, suggesting distinct neural underpinnings. Preliminary fMRI data underscored activation in known social cognition networks exclusively during social task engagements. Intriguingly, behavioral results showed only partial correlations across tasks, mainly between empathy and motion prediction, highlighting unresolved questions regarding the interconnectedness and specificity of social processing aspects. This research marks an initial stride toward comprehending social cognition comprehensively and disentangling its intricate interplay with general cognition. Such insights promise advancements in understanding social impairments and could furnish objective metrics for social cognition augmented by fMRI technology.

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BEHAVIORAL AND PHYSIOLOGICAL OUTCOMES OF ACUTE MATERNAL SEPARATION DURING EARLY LIFE

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Social ontogeny is the process by which an organism acquires necessary behaviors for survival and well-being among conspecifics. Social ontogeny is constrained by a critical developmental window in early life and has persistent implications for adult behavior. However, neither social behaviors, nor their underlying neural mechanisms, have been rigorously characterized during this window in animal models. Our laboratory recently determined that in P15 pups, a 3-hour period of maternal separation (MS) increases maternally-directed behaviors (MDBs) upon mother-pup reunion. Furthermore, acute MS activates hypothalamic oxytocin (OT) neurons, and OT receptor inhibition prevents MS-induced MDBs. Thus, OT system activation may drive increased MDBs following MS. In the current project, we investigated whether increased MDBs result from MS-induced metabolic stress, or from social isolation per se. We first reproduced our behavioral findings in a more ethological set-up, by performing automated behavioral analysis of mother-pup dyads with DeepLabCut. Next, we examined the effects of MS on metabolism. Intriguingly, maternally-separated pups did not show altered blood glucose or lactate levels, compared with unseparated controls. Metabolic stress is therefore unlikely to underlie OT activation and MDBs in this paradigm. Our future work will aim to further delineate metabolic events upstream of MS-induced behaviors during early life.

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Theta rhythmicity in the rat prefrontal cortex reflects preference among competing rewarding stimuli in a social context

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Competition between rewarding stimuli, such as social interaction and food is a common event. Yet, the mechanisms underlying decision making in such competition and its regulation by internal states are not fully understood. We aimed to explore neural activity in the rat prefrontal cortex during competition between social and food stimuli and to reveal the effects of social and food deprivation. Using chronically implanted multi-electrode arrays targeting various frontal brain areas, we recorded LFP signals from behaving rats during social vs. food discrimination task, at satiety, 24-hour and 48-hour food deprivation, occurring during isolation or group housing. Isolated rats continued to prefer social, as compared to food stimuli even after 24-hour food-deprivation, while grouped animals did not show any preference. Interestingly, grouped rats showed gradually increased theta power as the food deprivation was extended, while in isolated animals theta rhythmicity was higher from the beginning and was not affected by food deprivation. Similar results were found for the theta coherence between nucleus accumbens core and shell areas. Altogether, these results suggest that prefrontal theta rhythmicity reflects motivational competition as a function of the individual's internal state.

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Dopamine circuits underlying social interaction deficits in autism spectrum disorder

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Autism Spectrum Disorder (ASD) impairs social communication and reduces life expectancy. Previous work implicated the dopamine system in ASD. However, the underlying mechanisms through which dopamine influences social communication in ASD remain unclear. We hypothesize that specific subpopulations of VTA dopamine neurons mediate social behavior and might be disproportionately affected in ASD. If confirmed, this subpopulation could present a new therapeutic target for ASD treatments. To investigate the role of dopamine neurons in ASD, we established a hybrid SHANK3b-DATcre mouse line, which allowed us to monitor and manipulate neuronal activity in dopamine neurons in an ASD mouse model. Using the three-chamber social test, we validated this line for potential ASD-like behavior and social preference reduction. We found that SHANK3-DATCre mice replicate the social deficits found in SHANK3b mice including the previously documented sex differences. To characterize the differences in VTA dopamine neuron activity between SHANK3b mice and wild type (WT) mice we are using a miniature microscope that sits atop the mice's head and records dopamine activity with single-cell resolution. We couple this technology to various social interaction assays to obtain a comprehensive picture of how the brain's dopamine system underlies social behavior in both healthy and ASD-model mice.

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Other

THE ROLE OF THE INSULAR CORTEX IN THE ANTICIPATORY INSULIN RESPONSE

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The brain integrates external and internal sensory signals to track the body's current state. Anticipating challenges and preparing the body for them is essential for maintaining homeostasis.
A prominent example is the anticipatory physiological changes that prepare the body for food intake to improve metabolism, known as the cephalic phase response of digestion (CPRD).
Insular cortex (InsCtx) encompasses the "interoceptive cortex", sensing and modulating bodily functions. It is also a central node in the "salience network" which identifies relevant external cues. These two functions suggest its potential involvement in the CPRD. We focused on anticipatory cephalic phase insulin release (CPIR) and used chemogenetics and optogenetics to inhibit InsCtx. Both approaches suppressed the CPIR. We then used circuit mapping tools to reveal two candidate pathways from InsCtx to the brainstem region that regulates pancreatic insulin release (Dorsal Vagus Complex; DVC).
We identified a direct pathway (InsCtx-->DVC), and an indirect one through the Central Amygdala. We are currently performing pathway-specific optogenetic inhibition to test their functional relevance.
Disruption of interoception and CPRD have been linked to metabolic syndromes and psychiatric disorders. Our work could therefore help understand the underlying mechanisms and open new avenues for developing novel therapeutic approaches.

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Neurofeedback as a tool to explore the limits of brain activity control

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Our brain activity creates every aspect of our behavior and personality. But what is the limit of our control over this activity? To answer this question, we implement neurofeedback in mice.

This method uses live recording of brain activity across cortical networks combined with feedback to the animal of said activity. Brain activity is recorded using wide-field calcium-imaging, which produces a cortex-wide image of brain activity. The images are processed to produce live feedback.

The feedback in our system is the intensity of a LED the mouse is seeing: as the targeted brain activity changes – so does the LED intensity. When the intensity reaches 100%, the mouse is rewarded. As the mouse learns to achieve multiple rewards, the threshold of rewarded activity increases.

We exploit this system to investigate the flexibility of brain activity control by changing the rewarded activity patterns.

Our preliminary results show that mice are more successful in controlling activity in the primary somatosensory cortex compared to other areas. This is surprising as the activity in this area is presumed to be controlled by outside stimuli and not created by the mouse.Our eventual findings might contribute to further development of the existing neurofeedback methods for humans.

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Behavioral and neuronal signatures of adolescence in the mouse auditory cortex

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Adolescence is known to be a period of uncertainty, exploration, and learning. Our understanding of the underlying neural correlates of adolescence remains scarce. Here, we studied adolescence through the prism of auditory learning, and the neural representations of learned sounds in the auditory cortex of mice. We asked whether adolescent and adult mice discriminate tone categories differently, and how are these differences expressed in auditory cortical responses in behaving mice.
First, we trained freely behaving mice to perform a go no-go task of pure tone categories. We reveal weaker performance in adolescence compared to adulthood and found that it was attributed to specific biases.

Second, we trained head-restrained mice on the same task and performed two separate experiments: 1) We manipulated auditory cortex on a trial-by-trial basis using optogenetic silencing. Inhibiting auditory cortex in adult mice decreased performance, indicating a causal relationship between auditory cortex and tone categorization. 2) We recorded single units in the auditory cortex during engaged behavior using neuropixels.
We are currently evaluating the task-, stimulus- and choice-related activity in single neurons, as well as in population dynamics. Our aim is to reveal the neural correlates of behavior in adolescence as compared to adulthood.

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The association between mood and Heart Rate Variability: A meta-analysis

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Objectives: This ongoing meta-analysis aims to investigate the relationship between self-reported mood (SM) and heart rate variability (HRV). Previous meta-analyses highlighted lower HRV in clinically depressed individuals compared to healthy controls. This study will uncover the connection between subjective and objective mechanisms of depression. Methods: 11,475 studies utilizing self-reported mood and HRV were identified. Through systematic review and meta-analysis, these are being integrated to synthesize relationship between SM and HRV. Results: Results expected by October 2023. Possible results are either connection between SM and HRV, similarly to the relationship found in clinically depressed. On the other hand, if the relation between SM and HRV is found to be weak, it might suggest that SM is not a sufficient correlate for other broad physiological changes that underlie depression. Discussion: We aim to uncover valuable insights for research and clinical practice. The findings may indicate the potential use of HRV as an objective and continuous measure for tracking mood changes in healthy and depressed individuals. Furthermore, it could suggest the utilization of HRV biofeedback to improve mood. Conversely, if no significant correlation is found, intriguing questions arise concerning the fundamental mind-body connection in depression and the interplay between physical, and cognitive-emotional symptoms.

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Ketamine's Selective Influence on Cortical Pathways: Unraveling Anesthesia's Complexities.

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Understanding the mechanisms underlying anesthetic induced loss of consciousness remains a challenge. Recent research suggests that anesthetics modulate information integration and predictive coding in cortical neural networks. Ketamine, a dissociative agent, inhibits NMDA receptors and HCN1 channels, but its global impact on cortical network is unknown. To elucidate this, we studied ketamine's effects on post-synaptic responses in thalamo-cortical (TC) and cortico-cortical (CC) pathways, hypothesizing a preferential effect on CC responses. We directly measured excitatory post-synaptic potentials (EPSP) in auditory cortex (A1) layer 5 pyramidal neurons, following TC and CC stimulation. Preliminary results using 200uM of ketamine show a non-significant 5% increase in TC response amplitude, while the CC response amplitude is significantly reduced by 12.66% ($p<0.05$, Wilcoxon test). At a higher dose of 400uM, the TC response amplitude decreases by 15.38%, while the CC response amplitude is further reduced by 28.24% (both significant, $p<0.05$ and 0.001, respectively, Wilcoxon test). These findings indicate that ketamine preferentially inhibits CC responses over TC responses. This study sheds light on ketamine's impact on neural pathways, contributing to our understanding of consciousness and anesthesia mechanisms. It also generalizes previous findings with other anesthetic agents.

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EFFECTS OF ACUTELY SILENCING A THALAMOCORTICAL INPUT ON CANARY SONG SYNTAX

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How the brain flexibly controls the order of behavioral elements is yet to be discovered. Birdsongs are strings of well-defined vocal elements called syllables that provide excellent models to uncover how the brain controls the syntax of sequential behavior. The Magnocellular nucleus of the Anterior Nidopallium (MAN) is a part of the avian homolog of the cortico-basal ganglia-thalamo-cortical loop that innervates song-driving premotor nuclei. MAN's lateral part has been shown to control the variability of syllable acoustics, but the role of MAN's medial part (mMAN) is currently unknown. Our Preliminary work showed that chronic mMAN lesions in canaries, a species with flexible hierarchical song sequences, greatly affected syntax but minimally affected syllable acoustics. Here, we develop a chemogenetic approach to silence mMAN acutely. In contrast to the lesions in our pilot study, this method will allow us to control the time and area of neuronal silencing and to reduce the chance of off-target effects. The reversibility of chemogenetic silencing will afford excellent control for the effect of acute mMAN silencing on song syntax while .avoiding the long-term effect of chronic lesions

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Investigating brain responses towards emotionally-related climate change stories

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Objectives: Many people experience negative emotional reactions due to increasingly intense climate change. Previous studies of emotional phenomena related to climate change have focused primarily on worry and depression. In the present study, we investigated neural and subjective responses to those climate change emotions that we explored to be the most common in the general population: anger, compassion and hope. Methods: Individuals concerned about climate change were scanned using fMRI while listening to climate change stories that aimed to reactivate the above-mentioned emotions. The emotional stories were presented in a random order and were interspaced with neutral stories. Results: Preliminary fMRI results indicate that the emotional stories evoked brain responses in several regions that are implicated in emotion processing, such as limbic structures as well as sensory processing areas. These neural activations varied slightly depending on the type of emotion the stories evoked. Conclusions: The present results have important implications with regard to coping strategies and pro-environmental behaviors in populations who will increasingly come into contact with climate changes.

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NEWBORN REACTIONS TO MATERNAL PRENATAL STRESS ALTER UMBILICAL CORD BLOOD TRNA FRAGMENTS TARGETING CHOLINERGIC TRANSCRIPTS

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Maternal perceived prenatal stress (PPS) is a known risk factor for diverse developmental impairments in newborns, but the underlying molecular processes are incompletely understood. Here, we report that PPS responses altered profiles of blood transfer RNA fragments (tRFs), 16-50nt long non-random cleavage products of tRNAs at birth. Moreover, maternal and umbilical cord serum from stressed and control mothers and their newborns presented selective enrichment of particular tRF families grouped by their mitochondrial or nuclear genome origin, coded amino acid and cleavage type. Suggesting a sex-specific effect, grouped tRF families revealed

shared length and expression patterns which were strongest in the female newborns. Of those, some tRFs carried complementary motifs to specific cholinergic mRNAs, indicating possible translational regulation similarly to microRNAs. Compatible with the cholinergic regulation of stress reactions, those "CholinotRFs" achieved AUC of 95% when classifying female newborns according to maternal PPS. Correspondingly, we found altered catalytic activity of serum acetylcholinesterase, an effect which was elevated in male newborns, marking a second sex-specific impact. Our findings indicate association of tRF families' patterns with newborns sex-specific stress response to PPS, and may lead to better diagnosis and therapeutic tools for these and other stressors.

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MACHINE-LEARNING DEFINED MOTOR FEATURES UNTANGLE ATTENTIONAL LOADS IN VIRTUAL COGNITIVE-MOTOR TASKS

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Objectives: We utilize machine learning (ML) techniques to identify motor control features that are affected differentially by sustained visual attention (SVA) or divided attention (DA) tasks. Methods: A VR-CTT dataset from 144 participants was used (53 middle aged, 51 old and 40 young). Fifty-two scaled features (i.e., normalized by completion time) of 3D hand movements and simultaneous head rotations were defined (e.g., relative planning time, maximal hand velocity during movement execution). We utilized a logistic regression model to classify performance into two categories: SVA and DA. A total of 288 data points (144 SVA and 144 DA) were fed into the classifier. Results: The ML model achieved an accuracy of 92.5± 3.9%, with the following leading motor control features showing the most discriminative values: ratio between planning and execution durations of hand movements, planning duration variability, and the geometrical difference between ideal theoretical and actual performed path. Conclusion: This study reveals, for the first time, that hand kinematic features can be used to differentiate between SVA and DA tasks with high accuracy. The present methodology may lead to new diagnostic schemes for evaluating not only cognitive and motor abilities in isolation, but also the interactions between them.

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Dynamics and Regulation of Inter-Individual Behavioral Interactions in C. elegans Across Developmental Timescales

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Individuals within the same population dynamically change their social interactions across development. Understanding how these behaviors are modified across different stages of development and the neuronal processes involved remain unclear. Our lab developed a novel imaging setup to study the behavior of isolated C. elegans individuals at high spatiotemporal resolution and under controlled conditions. We expended our methods for simultaneous monitoring of multiple pairs of C. elegans across developmental timescales. We found that wild-type animals show dynamic patterns of social interactions across development that vary between pairs, with an overall increase in the average number of interactions throughout development. In addition, animals had longer duration of inter-individual interactions in the intermediate stages of development compared to early and late stages. Furthermore, by testing mutants with defects in mechano- and chemo-sensation, we found that specific sensory modalities are involved in organizing both the number of social interactions, as well as duration of interactions at specific stages of development. We are currently studying these behavioral changes between pairs of different sexes, as well as the effects of the social context on patterns of individuality. These results suggest the active role of sensory pathways in organizing complex patterns of social behavior across development.

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Orb2 Oligomerization in NPF Neurons as a Molecular Mechanism for Drive Accumulation in Drosophila

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Motivation is a neuronal representation of internal state that drives goal-directed behaviors, so that they are expressed at the right time, amount, and context. Though a lot is known about the neurobiology of motivation, how drives accumulate over time is unknown. A conceptual model explaining drive buildup, known as the hydraulic model for accumulation of drive, was raised by Nobel laureate Konrad Lorenz. According to this model, a physiological need, such as hunger, can be compared to fluid accumulating in a reservoir, creating pressure that drives behavior when the necessary resource, like food, is detected. Yet whether a biochemical mechanism that fits this model exists and its mode of action is largely unknown. This is because most studies in the field have focused on binary motivational states (i.e., deprivation and satiation), ignoring the gradual aspect of drives. Here we explore the hydraulic model at the molecular level in a subset of neurons that are known to regulate multiple drives (drosophila NPF system which is homologues to NPY system in mammals). We hypothesize that drive buildup may be encoded at the neuronal level, by the oligomerization of a potential drive factor, the prion-like protein Orb2 that undergoes physiological state-dependent aggregation that in turn regulates local protein synthesis synapses. Here we present experimental evidence that Orb2 oligomerization state regulates accumulation of drive. Preliminary results using fluorescence microscopy indicate that the differences between puncta in wt Orb2 flies tagged with GFP expressed in NPF neurons are significantly bigger than puncta of flies harboring a point mutation in Orb2 that dramatically reduces its oligomerization capacity (Orb2F5Y). Moreover, the differences between those flies were studied in MST and showed a difference in its kinetics implied that small molecules behave differently in hotter regions than bigger ones (monomers versus oligomers). Next, flies expressing wt Orb2 tagged with GFP in NPF neurons were starved for 16 or 20 hours. Interestingly, the fluorescence of starved flies was higher in specific subset of NPF neurons (P2) suggesting that they are related to hunger drive. Taken together, these results provide promising evidence for the role of Orb2 in encoding drive level. Studying mechanisms encoding graded response as opposed to binary outcomes, may transform how we think about natural and pathologic variation in human behavior, from altering one's metabolic set point, to dialing up and down the range of responses.

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Mixed connectivity and local computations across a whole adult Drosophila brain

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Mapping connections between neurons can be achieved by analyzing electron microscopic images of the brain. Recently, a comprehensive neuronal wiring diagram of an entire adult female Drosophila melanogaster brain was published, detailing 139,255 neurons and approximately 50 million chemical synapses. While the brain can be represented as a network of nodes (neurons) connected by edges (synapses), neurons themselves possess complex morphologies, and these morphological details influence network computations. In this study, we examined the distribution of presynaptic and postsynaptic terminals within individual cells across the connectome and discovered that many Drosophila neurons exhibit mixed connectivity. This means they contain presynaptic terminals within dendrites and postsynaptic terminals within axons. Although axo-dendritic synapses—presynaptic axons connecting to postsynaptic dendrites—are predominant, other types, such as axo-axonic and dendro-dendritic synapses, are also prevalent. We identified that approximately 10% of neuron-neuron connections are axo-axonic and 3% are dendro-dendritic. These non-canonical connections vary depending on brain region, cell type, neurotransmitter, and the morphology of pre- and postsynaptic partners. Our detailed analysis suggests that non-canonical connections frequently participate in local recurrent circuits and that localized segregation of pre- and postsynaptic terminals occurs within dendritic and axonal trees. Together, our whole-brain connectome analysis highlights the complexity of neural connectivity, indicating that non-canonical connections are widespread and may play a key role in local computations.

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Learning like Infants Boosts Efficiency and Generalization in Learning Social Prediction Tasks

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Early in development, infants learn a range of useful concepts that can be challenging from a computational standpoint. Early learning includes an initial understanding of aspects of concept meaning, such as implications, causality, and their use in predicting future events. This is often achieved with little supervision and from relatively few examples compared with current network models. In learning about objects and human-object interactions, early-acquired concepts are often used to support the learning of additional concepts. In this work, we model how early-acquired concepts are used in learning subsequent concepts and compare the results with standard deep network modeling. We focus on the concepts of animacy and goal attribution in learning to predict future events. Our findings show that using early concepts in learning new ones leads to better learning (higher accuracy) and more efficient learning (less data). This integration also shapes the representation of the acquired concepts. When concepts were learned in a human-like manner, the resulting representations were more useful, improving generalization to novel data and tasks. On a broader level, the results suggest basic differences in the conceptual structures acquired by current network models and human learning, with implications for training network models.

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Control of Vibrissa Movement by Touch During Active Sensing

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The sensors in the somatosensory system of the rodents, the vibrissae, are embedded in the motor plant, move when intrinsic muscles contract, and bend upon touching an object. This contact triggers firing of touch cells in the trigeminal ganglion (TG), that excite neurons in the trigeminal nuclei (TNs) in the brainstem. These neurons innervate motoneurons in the facial nucleus (FN) and premotor neurons in the vIRt nucleus, which also send periodic input to the FN. To evaluate the effects of feedback connections on vibrissa movements, we construct and analyze a neuro-mechanical model of the brainstem loop. The model describes the TN, FN, and vIRt activity, as well as the connections between all populations, based on a rate model. It includes simplified, quasi-static descriptions of the vibrissa as an elastic beam, the motor plant as springs, dampers, and muscles, and a simplified mechano-to-neuro transformation in the TG grounded in experimental observations. We find that the delay in the brainstem loop, along with connection strength and adaptations, controls the ability of inhibitory TN->FN connections to briefly reduce FN neuron firing, leading to a “touch-induced pump” where the vibrissa momentarily retracts during protraction.

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Direction-dependent dissimilarity of fingers fine-motor control in subacute stroke patients

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Humans possess the ability to make selective use of their fingers. This ability is impaired following a stroke. Neurological observations showed that people with hemiparesis due to stroke affecting M1 or the corticospinal tract, usually exhibit greater difficulty opening their paretic hand than closing it. This observation is attributed to the loss of finger individuation ability, often referred to as enslavement, (i.e., the unwanted coactivation of non-intended fingers in individuated finger movements). However, previous studies were based on assessments of individuation ability by examining the total sum of enslavements of the non-instructed digits1. Although this individuation index is largely immune to the weakness of the fingers, it lacks the capacity to capture the full range of finger control. In addition, it overlooks the similarity of the force patterns in stroke relative to the healthy population. Here we sought to characterize the full capacity of finger control in acute and sub-acute poststroke compared to aged-matched healthy participants. We recruited a cohort of 45 hemiparetic stroke patients with first-event unilateral ischemic (11 females; age 60.9±10.1 years; time after onset 41.4±16.6 days) and 11 healthy age-matched controls (6 females; age 56.3±10.0 years). Participants performed a robotic-based individuation task with their paretic hand. In each trial, participants were instructed to move a single digit in one direction toward a force target. Participants repeated the task separately for each direction (flexion and extension) and in four different force levels (20%, 40%, 60% and 80% of maximal voluntary contraction force, MVF). Here, we used functional principal component analysis (fPCA) to estimate the Mahalanobis distance (MD) of patients' finger force patterns from the reference healthy population and to assess the quality of finger control during flexion and extension finger movements. MD is large when the pattern is impaired (i.e., it is dissimilar to the healthy controls) and small when the force pattern is similar to healthy controls. Our results show that finger force patterns in stroke patients present distinctly different shapes across direction and force levels. Repeated-measure 2-way ANOVA reveals significant direction effect ($F_{1,44}= 4.72$, $p=0.035$), significant force level effect ($F_{3,132}= 3.6$, $p=0.015$) and significant direction×force interaction ($F_{3,132}= 3.25$, $p=0.024$). Post-hoc analysis revealed that the main differences across force directions in the MD measure was driven by differences at low force ($t_{45}= 3.96$, $p=0.001$). The stroke patients' main group was divided into two subgroups according to the Fugl-Meyer (FM) clinical test. Although this dissimilarity in

finger control was larger in severe patients (FM≤40, n=19) compared to milder to moderate patients (FM>40), both groups showed similar force-dependent difference across flexion and extension direction. Our data suggest that the quality of finger control in stroke patients distinctly differs from the healthy population mainly at low forces. 1. Xu, J. et al. Separable systems for recovery of finger strength and control after stroke. Journal of Neurophysiology 118, 1151–1163 (2017).

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High Cognitive Violation of Expectations is Compromised in Cerebellar Ataxia

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While traditionally considered a motor structure, the cerebellum is also involved in cognition. However, the underlying cognitive mechanisms through which the cerebellum contributes to evolutionarily novel cognitive abilities remain poorly understood. Another open question is how this structure contributes to a core unifying mechanism across domains. Motivated by the evolutionary principle of neural reuse, we suggest that a successful account of cerebellar contributions to higher cognitive domains will build on the structure's established role in motor behaviors. We conducted a series of neuropsychological experiments, assessing selective impairments in participants with cerebellar ataxia (CA) compared to neurotypicals in solving sequential discrete problems. In three experiments, participants were asked to solve symbolic subtraction, alphabet letter transformation, and novel artificial grammar problems, which were expected or unexpected. The CA group exhibited a disproportionate cost when comparing expected problems to unexpected problems, suggesting that the cerebellum is critical for violation of expectations (VE) across tasks. The CA group impairment was not found either when the complexity of the problem increased or in conditions of uncertainty. Together, these results demonstrate a possible causal role for the human cerebellum in higher cognitive abilities. VE might be a unifying cerebellar-dependent mechanism across motor and cognitive domains.

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