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Alexander Thiele, Newcastle University, UK
Cerebellar Climbing Fibers Exhibit Reward Prediction Signals in both Operant and Classical Conditioning Tasks

Court Hull, Dept. of Neurobiology, Duke University

Classical models of cerebellar learning posit that climbing fibers operate according to a supervised learning rule to instruct changes in motor output by signaling the occurrence of movement errors. However, recent evidence has challenged this view by suggesting that climbing fiber-driven complex spiking can exhibit characteristics consistent with a reinforcement learning rule in an aversive classical conditioning paradigm. To test whether sensory prediction error provides a generalizable model to explain the activity of climbing fibers in other behaviors and across other cerebellar regions, we have measured complex spiking in head-fixed mice in two reward-driven behavioral paradigms. First, we trained mice to associate a visual cue with an upcoming reward and measured complex spiking both at the population level and within individual Purkinje cell dendrites before and after learning. These data suggest that individual climbing fibers can signal distinct task features before and after learning, and likely signal reward expectation. We then trained mice on a second task in which they must execute a properly timed forelimb movement to receive reward. Population and single dendrite imaging during task performance revealed similar rules as seen during the classical conditioning paradigm in which climbing fibers have stronger activity under conditions in which rewards are expected. However, there was no evidence for the climbing fibers encoding negative reward prediction errors, as required by most reinforcement learning models. Hence, these data reveal key features of cerebellar CF activity that differ significantly from many classically studied cerebellar behaviors, and suggest an extension to current models of cerebellar learning in order to account for the role of complex spiking in behaviors where reward is expected.
Pogz deficiency leads to abnormal behaviour and transcriptional dysregulation in the brain

Reut Suliman

Background

De-novo loss-of-function mutations in POGZ (Pogo Transposable Element with ZNF domain) were identified in multiple individuals with developmental delay, half of them with a diagnosis of autism spectrum disorder (ASD). POGZ consistently interacts with the three isotypes of HP1 and therefore may play a key role in transcription regulation. As of today, the molecular, cellular and neuronal mechanisms through which POGZ is associated with ASD remain incompletely understood.

Objectives

Our overall aim was to delineate the function of POGZ in the normal brain and in ASD. In particular, we inquired how rare genetic insults in this gene influence networks of genes leading to ASD.

Methods

Our approach to study the function of POGZ was based on Pogz-deficient mice. We used a conditional knockout mice that harbor a homozygote Pogz knockout restricted to the brain (Pogz cKO\(^{-}\)). To characterize the anatomical and behavioural phenotypes we used several staining methods and a battery of behavioural assays relevant to ASD. To explore how POGZ modulates gene expression in the brain and identify its transcriptional targets we used RNA-Seq and dual-luciferase reporter assay.

Results

Pogz deficient mice showed a significant growth delay relative to their Control littermates. Behaviourally, these mice exhibited impaired sociability, deficits in motor learning and olfaction.

Similar to what was reported in humans, the cKO\(^{-}\) mice were “overly friendly”. To identify defects in neural development that may explain the behavioral phenotypes, we first studied brain anatomy, including the structure of the cortex and distribution of neuronal markers, but found that Pogz-deficient mice displayed no detectable defects. However, adult neurogenesis was significantly decreased in the hippocampus because of reduced neuronal survival. Gene expression profiling of the hippocampus and cerebellum identified a large number of
upregulated genes that are enriched for axon guidance and regulation of locomotion. Since POGZ was found to be an integral part of the HP1 protein complexes, and given the gene expression results, we hypothesized that POGZ plays a key role in transcription repression. Indeed, dual-luciferase reporter assay showed that POGZ acts as a negative regulator of transcription through its interaction with HP1 proteins.

Conclusions

Our study shows that Pogz deficiency in mice is sufficient to cause ASD-related behaviours, similar to those found in human individuals with de-novo mutations in POGZ. The behavioral abnormalities and growth delay may result from lower survival of newly born neurons and transcriptional dysregulation in mature neurons caused by POGZ deficiency.
Autistic-like behavior and Purkinje cell dysfunction in Pogz mutant mice

Ben Title

Autism spectrum disorder (ASD) is a prevalent neurodevelopmental disorder characterized by impaired social interaction, communication deficits and repetitive or restricted behaviors. Disruptive mutations in pogo transposable element-derived protein with zinc finger domain (POGZ) gene were found to be associated with ASD and intellectual disability (ID). In humans, POGZ is highly expressed in the cerebellum, which is considered to have a primary role in the pathophysiology of ASD. Despite the abundant evidence supporting the involvement of the cerebellum in ASD, little is known about the functional physiology of the cerebellum in the disorder and whether changes in cerebellar function have a significant behavioral impact.

Here we evaluate the possibility that the cerebellum represents a critical locus of ASD-like pathophysiology in mice lacking Pogz. We first characterize how Pogz knock out (KO) affect ASD-related behavior in mice. We found that loss of Pogz in the mouse brain results with ASD-like social impairments, abnormal repetitive digging and motor coordination deficits. We then investigated the electrical activity in the cerebellum of Pogz-deficient mice. We found that Pogz-deficient mice have a lower spontaneous firing frequency of both simple spikes (SS) and complex spikes (CS) in cerebellar Purkinje cells (PCs). Furthermore, SS and CS firing frequency gradually decreased as a function of Pogz-deficiency levels. Since PCs did not show significant differences in their intrinsic properties, we conclude that the observed reduction in spontaneous firing rate is probably due to alterations in the neuronal circuitry.

Together, these data highlight the importance of POGZ for cerebellar function and support a model by which cerebellar pathology may account for ASD-related behaviors.
Impaired sensorimotor synchronization in autism reveals slow updating of internal priors

Gal Vishne

Autism is characterized by deficits in social communication and by repetitive patterns of behavior, interests and activities. Much attention has been put on the social aspect of the disorder, but in recent years there is growing understanding that atypical sensory processing and motor deficits are core to the disorder. Recent findings show that individuals with autism underuse previous environmental information in making perceptual decisions relative to neurotypical individuals. This finding has been interpreted within a Bayesian framework, but in different ways: According to one hypothesis individuals with autism over-estimate volatility of the environment (Lawson et al., 2017), therefore they are expected to track adequately fast environmental changes, and underuse knowledge acquired over a long time. By contrast, according to the slow updating account (Lieder et al., submitted) they are expected to track changes slowly but adequately accumulate information over long durations. We compared these conflicting predictions by measuring sensorimotor synchronization (finger tapping) to an external metronome with both fixed and alternating tempos. Performance in finger tapping is characterized by: (a) phase (asynchrony) – the temporal interval between the metronome beat and the participant’s response (b) period – participant’s inter-response-interval. Participants with autism showed substantially higher phase variability and higher correlation between consecutive phases, reflecting impaired error-correction over short intervals. In the alternating tempo conditions, individuals with autism did not adapt their phase to the changes, while they did adapt their period. This dual pattern reveals impaired error-correction immediately following the change and adequate period updating, which is a slower mechanism (Repp 2001). The impairment in online error-correction along with adequate slower period correction supports the slow updating Bayesian account of autism and is in line with behavioral reports of the difficulties individuals with autism face when the environment changes abruptly.

Advisor: Prof. Leon Deouell (this work is with Prof. Merav Ahissar)
Behavioural consequences of neural coding development

Lilach Avitan

During early life the neural code must develop to appropriately transform sensory inputs into behavioural outputs. However little is known about how developments in neural representations directly impact behaviour. By combining behavioural analysis with 2-photon calcium imaging at multiple timepoints of developing zebrafish larvae we show that (i) there is a spatial shift in prey detection which is mirrored by a developmental shift in tectal neural activity, (ii) the similarity between evoked and spontaneous activity patterns decreases over development, contrary to the trend previously observed in mammals, and (iii) decoders of spatial position from neural activity improve their performance over development, and remarkably can predict individual differences in prey-capture behaviour. Together these results show that developmental signatures of an emerging neural code can be directly related to observable properties of behaviour.
Deciding when to abandon a resource to explore elsewhere is a key component of foraging behavior. A solution to this problem comes in the form of the marginal value theorem (MVT), which states that in order to maximize returns, an optimal forager ought to leave its current site whenever the immediate rate of reward drops below the average rate. However, this elegant solution to the foraging problem only applies in deterministic environments, in which both immediate and average reward rates are knowable to the animal. In the more realistic stochastic scenario, where not every attempt at reward is successful, the immediate reward rate is ill-defined and the marginal value theorem does not apply.

Here, I will present two related studies looking into mouse foraging behavior under uncertainty. In these tasks, mice exploit resource sites by nose poking for probabilistic rewards. A general theoretical analysis suggests that mice should decide when to leave a given port by accumulating evidence that it is depleted by counting non-rewarded actions. To maximize reward intake, they should do so at a rate set by the statistics of the environment, including the probabilities of reward delivery and depletion as well as the travel time between sites. Interestingly, we found that leaving decision were in agreement with these predictions on trial-by-trial bases, and, when averaged across trials, also with MVT’s predictions.

These results suggest that mice naturally optimize probabilistic foraging decisions in an efficient manner and that therefore this class of tasks can provide a rich and efficient paradigm to study evidence accumulation processes in general.
Mapping human white matter tracts using multi-modal quantitative MRI

Roey Schurr

Diffusion MRI (dMRI) tractography algorithms reconstruct streamlines that represent the underlying white matter (WM) fascicles, allowing to study the human connectome in vivo. Yet (1) Some recovered streamlines do not correspond to true fascicles (false positives) and (2) grouping multiple streamlines together to identify a specific WM tract is still challenging. Many fiber clustering methods are based on anatomical landmarks or fiber termination points, but these fiber properties are not well-captured by current tractography algorithms. A major source contributing to this difficulty is the inherent ambiguity in the dMRI signal. Different fascicle configurations can give rise to the same dMRI signal at the voxel level, and any local error in fiber tracking can propagate and lead to global effects in tractography results. More information is therefore required to disambiguate the dMRI signal and obtain a more accurate mapping of the long range WM projections.

The goal of the presented works is to test the hypothesis that tractography results can be optimized by introducing complementary information derived from other quantitative MRI (qMRI) measurements, specifically quantitative T1 mapping.

Here we show that T1 mapping can be used for accurate identification of specific WM tracts. First, we show that invalid tractography results of the optic radiations can be eliminated using T1 mapping, echoing a known result from histological myelin staining studies. Second, we developed a framework for qMRI-based tract identification. We show that the vertical occipital fasciculus (VOF) can be separated from the nearby posterior arcuate fasciculus based on their T1 signatures. We further tested the correspondence between the estimated cortical projections of the VOF and two cortical parcellations – functional and cytoarchitectonical. Finally, we generalized this approach to a third WM system, the superior longitudinal fasciculus (SLF).

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

Advisor: Dr. Aviv Mezer
Modelling conduction delays in the corpus callosum using MRI-measured g-ratio

Shai Berman

Background: Conduction of action potentials along myelinated axons is affected by the axon’s structural features, such as its g-ratio. The g-ratio is the ratio between the inner and outer diameters of the myelin sheath surrounding the axon. The effect of g-ratio variance on conduction properties has been quantitatively evaluated using single-axon models. Empirical values of g-ratio and conduction time are often measured using invasive techniques such as electron microscopy or electrical recordings, respectively. It has recently become possible to estimate a g-ratio weighted measurement using quantitative MRI. Nevertheless, it is still unclear whether the variance in g-ratio in the healthy human brain will lead to significant differences in conduction velocity. In this work we test whether the g-ratio MRI measurement can be used to predict conduction delays in the corpus callosum.

Results: We present a novel framework in which the structural properties of fibers (i.e. length and g-ratio, measured with MRI), are incorporated in biophysical models of axon conduction, to predict conduction delays of long-range white matter (WM) fibers. We apply this framework to the corpus callosum, and find that it produces conduction delays which are compatible with values generated in more direct measurements (~15 ms).

Furthermore, we compare young and old subjects, since studies that used response time and electrophysiology suggest an increase in conduction delays with age. We ask whether there are differences in the g-ratio and length between the age groups, and whether they will lead to a difference in conduction delays. We find small to no significant differences between the groups’ predicted delays.

Conclusions: Our study provides a framework for predicting conduction latencies in vivo. The framework could have major implications for future studies of WM diseases or large range network computations. Our results highlight the need for improving in vivo measurements of WM microstructure.

Advisor: Prof. Aviv Mezer
Looking beyond Frequency: The Effect of Entropy on Language Learning

Ori Lavi-Rotbain

Frequency effects are prevalent across many aspects of language learning and processing (e.g. more frequent words are acquired earlier and are easier to process). However, frequency alone does not tell us about the entire distribution of words (e.g. how predictable the input is overall). Here, we focus Shannon’s Entropy, a measure that quantifies how unpredictable a variable is and therefore tells us something about the entire distribution of words. In the past decade, there has been growing evidence for the impact of measures like entropy on language structure and use. However, very little work to date has looked at the impact of entropy on learning novel linguistic information. In a series of studies we asked if entropy reduction would lead to better learning.

First, we looked at the natural linguistic input children receive and found that words in this speech style have a Zipfian distribution (similar to speech directed to adults). This is a highly skewed distribution with relatively small entropy. However, while the natural input to language learners is non-uniform, most artificial language experiments use a uniform distribution of items. Uniform distribution are the least predictable and hence may impede learning. In a large scale study we compared learning from different levels of entropy (entropy was reduced by making one word more frequent than the rest) and found that entropy reduction is beneficial for both adults and children. In a second study we found that children’s segmentation and recognition of words with low frequency are facilitated by low entropy. Our results highlight the role of entropy in language learning and open up new research directions on the impact of entropy on real-life language learning.

Advisor: Prof. Inbal Arnon
Efficient coding and language evolution: The case of color naming

Noga Zaslavsky

We derive a principled information-theoretic account of cross-language semantic variation. Specifically, we argue that languages efficiently compress meanings into words by optimizing the Information Bottleneck (IB) tradeoff between the complexity and accuracy of the lexicon. We test this proposal in the domain of color naming. First, we show that the IB principle can integrate perception and communicative need in generating efficient coding schemes that compress percepts into words. Second, we show that color-naming systems across languages achieve near-optimal compression, as predicted by IB, and that the optimal IB systems explain much for observed cross-language variation. Third, we show that the IB systems evolve through a sequence of structural phase transitions, in a process that synthesizes continuous and discrete aspects of previous accounts of color category evolution. This suggests that languages may evolve under pressure to remain near the theoretical limit of efficiency. To test this hypothesis directly, we obtained diachronic color naming data from the language Nafaanra, spoken in western Ghana. We show that color naming in Nafaanra has changed over the past several decades in a way that supports our predictions. Finally, the principle we invoke is not specific to color, and initial results from other semantic domains suggest that it may apply to cross-language semantic variation more generally.

Advisor: Prof. Naftali Tishby
The Choice Engineering Competition

Ohad Dan

In psychology, economics and neuroscience, there is a longstanding interest in the principles underlying decision-making and the ways by which these principles can be used to bias human choice. *Choice architecture*, a term coined by Nobel prize laureate Richard Thaler, utilizes qualitatively-defined psychological principles to make qualitative changes to behavior. In contrast, quantitative models of human’s choice are routinely used in the field of operant learning. These later models have the potential to revolutionize the field of choice architecture into *choice engineering*, defined as the use of quantitative models to shape behavior. Are current models of choice accurate enough to successfully engineer behavior?

To address this question, we announce The Choice Engineering Competition. The challenge presented to the researchers participating in the competition is to propose an allocation of 25 binary rewards to each of the alternatives in a 100-trials two-alternative, forced-choice experiment, that maximally biases the choices of human subjects towards one of the alternatives. The winners of the competition are those participants whose reward schedules maximize the empirical bias as would be tested from behavior of thousands of subjects. The competition offers two participation tracks. In the first “static” track, choice designers are invited to propose a sequence of rewards that associate the rewards, in advance, to specific trials. In the second “dynamic” track, choice designers are challenged to submit a computer program that allocates, in every trial, the reward/s of the next trial, based on the history of choices and rewards. Our numerical simulations suggest that effective engineering of behavior requires an accurate behavioral model which matches the policy decision makers actually utilize in the experiment. In this sense, choice engineering is a novel way of comparing models. Moreover, the competition allows to compare between quantitative models with arbitrary complexity and qualitative models which rely on heuristics.

Advisor: Prof. Yonatan Loewenstein
Blood-brain barrier dysfunction in aging induces hyper-activation of TGF-beta signaling and chronic yet reversible neural dysfunction

Daniela Kaufer, Dept of Integrative Biology and Helen Wills Neuroscience Institute, UC Berkeley

Aging involves a decline in neural function that contributes to cognitive impairment and disease. However, the mechanisms underlying the transition from a young-and-healthy to aged-and-dysfunctional brain are not well understood. Here, we report breakdown of the vascular blood-brain barrier (BBB) in aging humans and rodents, which begins as early as middle age and progresses to the end of the lifespan. Gain-of-function and loss-of-function manipulations show that this BBB dysfunction triggers hyperactivation of transforming growth factor β (TGFβ) signaling in astrocytes, which is necessary and sufficient to cause neural dysfunction and age-related pathology. Specifically, infusion of the serum protein albumin into the young brain (mimicking BBB leakiness) induced astrocytic TGFβ signaling and an aged brain phenotype including aberrant electrocorticographic activity, vulnerability to seizures, and cognitive impairment. Furthermore, conditional genetic knockdown of astrocytic TGFβ receptors, or pharmacological inhibition of TGFβ signaling, reversed these symptomatic outcomes in aged mice. Finally, we found that this same signaling pathway is activated in aging human subjects with BBB dysfunction. Our study identifies dysfunction in the neurovascular unit as one of the earliest triggers of neurological aging, and demonstrates that the aging brain may retain considerable latent capacity which can be revitalized by therapeutic inhibition of TGFβ signaling.
The Teacher-Scholars Program: Combining high-end research with STEM education in Jerusalem

The Teacher-Scholars Program is a unique project, aimed at advancing high-school level STEM (Science, Technology, Engineering and Math) education, while enabling PhD postgraduates, who are passionate both about research and about teaching, to combine these two passions. This program attracts high level science teachers into the schools and brings technology and scientific leadership from the academic world into the school system while providing a backbone of research excellence in the university.

The Teacher-Scholars program injects the education system with a cadre of new, energetic, and highly qualified and motivated science teachers, who will not only be continually updating their science knowledge through their research, but also provide their pupils with an essential window into the world of research.

The Teacher-Scholars program, has been training and mentoring science doctoral postgraduates as high-school science teachers in Jerusalem for the past five years. The teachers work half-time in high schools, while continuing to work in parallel as research associates in research labs at the Hebrew university. This combination creates a new career path, which enables its members to divide their time between these two worlds of research and education. It is also synergistic: the science aspect is manifest at school, through many extracurricular activities, in which the pupils of program members are exposed to academia and to science research; In parallel, the university research labs also profit from the program as they gain long-term, highly qualified researchers, who serve as knowledge centers in the labs. Currently the program consists of 12 HUJI teacher-scholars, who teach over 650 pupils in 11 different high-schools. The program is supported by all participating entities including HUJI, Municipality of Jerusalem, JDA, The Trump foundation, and the Ministry of education, and provides a supported long-term employment for its members.
The "creatures" of the human cortical somatosensory system

Noam Saadon-Grosman

Penfield’s description of the “homunculus”, a “grotesque creature” with large lips and hands and small trunk and legs depicting the representation of body-parts within the primary somatosensory cortex (S1), is one of the most prominent contributions to the neurosciences. Since then, numerous studies have identified additional body-parts representations outside of S1. Nevertheless, it has been implicitly assumed that S1’s homunculus is representative of the entire somatosensory cortex. Therefore, the distribution of body-parts representations in other brain regions, the property that gave Penfield’s homunculus its famous “grotesque” appearance, has been overlooked. We used whole-body somatosensory stimulation, functional MRI and a new cortical parcellation to quantify the organization of the cortical somatosensory representation. Our analysis showed first, an extensive somatosensory response over the cortex; second, that the proportional representation of body-parts differs substantially between major neuroanatomical regions and from S1, with, for instance, much larger trunk representation at higher brain regions, potentially in relation to the regions’ functional specialization; and finally, that selectivity and laterality in somatosensory representation decreases gradually peripherally from S1, suggesting hierarchical processing along three distinct neuroanatomical pathways. In combination, these results extend Penfield’s initial findings to the higher level of somatosensory cognition, and suggest a major role for somatosensation in human cognition.

Advisors: Prof. Yonatan Loewenstein and Prof. Shahar Arzy
Stabilizing the grid cell representation by coupling modules through recurrent synaptic connectivity

Noga Mosheiff

Grid cells in the entorhinal cortex encode the position of an animal in its environment with spatially periodic tuning curves of varying periodicity. Recent experiments established that these cells are functionally organized in discrete modules with uniform grid spacing. Furthermore, several experiments support a theoretical proposal, that within each module neural activity is constrained by recurrent connectivity to lie within a two-dimensional continuous attractor. Yet, not much is known about synaptic connectivity between cells from different modules. Here we argue that coupling between grid cell modules is essential in order to maintain the code stability, in the absence of sensory cues that inform the animal about its absolute position. The state of each module might be perturbed by noise that arises intrinsically within the module or by noise in the velocity inputs, leading to gradual drift in the represented position in each module. However, to avoid catastrophic readout errors and obtain a continuous joint representation of position over time, the drifts in different modules must be compatible. Here we develop a theory of coupled grid cell modules, each modeled as a continuous attractor network. We identify a simple scheme to approximately read out the drift velocity in each module. Using this scheme we propose a way to couple the drift velocities of different modules which can be implemented by plausible neural circuitry. As a result of the coupling, the activities of the different modules shift together, with a relative chosen velocity ratio that defines the grid spacing. This method eliminates the relative drift driven by the external input, and reduces the relative drift driven by the neuronal noise. Our results suggest that recurrent connectivity between grid cells belonging to different modules may help stabilize the grid cell representation of position.

Advisor: Prof. Yoram Burak
Cellular mechanisms of auditory surprise in detailed model of cortical microcircuit

Oren Amsalem

The nervous system is notorious for its strong response to a “surprise” – an input that deviates significantly from an expected stimulus. One manifestation of such a surprise-response is the stimulus-specific-adaptation (SSA), whereby the neuronal response is reduced for a repeated stimulus (the “standard”) but not (or less so) for a rare stimulus (the “deviant”). We explored the mechanisms underlying SSA in auditory cortex using a dense computer-generated neocortical network of a ~0.3 mm³ composed of ~31,000 cells and ~36 million synapses. This circuit includes the physiological characteristics of excitatory and inhibitory synapses and the spikes patterns for the 55 cell types comprising this 6-layered circuit. We simulated SSA by activating 574 tonotopically-mapped thalamic afferents impinging on this network; the response of each axon was fitted to experimental results in the rat. Our simulated circuit generated SSA response that was similar to that found experimentally. We uncovered three-key mechanisms underlying the emergence of SSA: synaptic depression (which is the typically assumed to be the key mechanism for SSA), spike frequency adaptation (SFA) and network connectivity. The relative contribution of each of these mechanisms was explored, and its underpinning was explained. We concluded that the fine-scale reconstructed cortical microcircuit provides a powerful predictive tool for uncovering emergent cortically-based phenomena. We plan to use this “canonical” cortical microcircuit to explore a variety of open questions related to the mechanisms underlying cortical phenomena in other modalities, such as the emergent of “salt and pepper” receptive field organization in mouse visual, auditory and, somato-sensory cortices.

Advisor: Prof. Idan Segev
Coherent Chaos in a Recurrent Network with Structured Connectivity

Itamar Daniel Landau

Neural activity observed in the neocortex is temporally variable, displaying irregular temporal fluctuations at every accessible level of measurement. Furthermore, these temporal fluctuations are often found to be spatially correlated whether at the scale of local measurements such as membrane potentials and spikes, or global measurements such as EEG and fMRI. A thriving field of study has developed models of recurrent networks that intrinsically generate irregular temporal variability, the paradigmatic example being networks of randomly connected rate neurons which exhibit chaotic dynamics. These models have been examined analytically and numerically in great detail, yet until now the intrinsic variability generated by these networks have been spatially uncorrelated, yielding no large-scale coherent fluctuations. Here we present a simple model of a recurrent network of firing-rate neurons that intrinsically generates spatially correlated activity yielding coherent fluctuations across the entire network. The model incorporates random connections and introduces a structured component of connectivity that sums network activity over a spatial “output” mode and projects it back to the network along an orthogonal “input” mode. We show that this form of structured connectivity is a general mechanism for producing coherent chaos.

Advisor: Prof. Haim Sompolinsky
Training-dependent two-way plasticity in the motor cortex of the adult monkeys.

Ankur Gupta

The adult brain undergoes systemic changes in response to sensory stimuli, recovery from injury and during motor skill learning. In this study, we identify the organizational changes in the motor cortex following skill learning. The experimental paradigm comprised of sequentially training 3 monkeys on two types of center out target acquisition tasks (and 2 monkeys on single task) that required different joints engagement and muscle recruitment: isometric (ISO) task (requiring wrist and finger torques) and reaching (KIN) task (requiring shoulder and elbow movements). Motor cortical maps were obtained in each monkey after extensive training in each task. In parallel, neuronal firing pattern was also recorded in each of the tasks. The data collected comprised of isometric (n=693) and reaching (n=550) sites. We found that learning a motor task that engages a specific set of joints (either distal joint, or proximal joint) led to expanded representation of these joints. In monkeys performing ISO task distal joints comprised 67.38% of the total motor cortex (65.76% in M1) while in those performing KIN task, distal joints comprised only 39.43% of the total motor cortex (42.81% in M1). In ISO to KIN task paradigm, distal to proximal shift was 61% and proximal to distal shift was 10%, whereas, in KIN task to ISO task paradigm, distal to proximal shift was 13% and proximal to distal shift was found to be 59%. However, the fraction of task-related and/or directly tuned cells was constant irrespective of the performed task. These findings suggest that motor cortical plasticity is an extensive and general property, which is both symmetric and reversible over the course of few months. We further suggest that the emergence of directional tuning is independent of cortical maps and is not subjected to similar remodeling processes. Hence, this study indicates that the cortical mapping is task dependent and the directional tuning of the neurons is not.

Advisor: Prof. Yifat Prut
Transfer RNA-derived fragments as putative drivers of ischemic stroke recovery

Katarzyna Winek

Ischemic stroke is a major cause of death and disability worldwide and its incidence elevates with prolonged life expectancy, but the patho-mechanisms involved in post-stroke recovery are largely unknown. Here, we report that fragments derived from transfer RNA (tRFs), which were recently discovered as biologically active entities, may contribute to the recovery from ischemic stroke. tRFs may be readily produced from pre-existing tRNA chains by the angiogenin nuclease, known to elevate post-stroke. Functionally, tRFs may be mechanistically reminiscent of microRNAs (miRs), suppressing the expression of target mRNAs with complementary sequence motifs, or alternatively interact with specific proteins and/or modulate transcription.

In search for tRFs involvement in post-stroke recovery we subjected whole blood RNA from 38 patients 2 days post-stroke and 10 age-matched controls to short RNA-sequencing. Both miR and tRF changes emerged, especially in RNAs carrying complementary sequence motifs to cholinergic transcripts. Segregating tRFs and miRs into inter-related modules by weighted gene co-expression network analysis (WGCNA) revealed putative links between their modified levels, innate immunity changes and functional post-stroke recovery 3 months later, indicating that these changes could potentiate the cholinergic blockade of post-stroke immune activities and modulate recovery. To challenge this prediction, we sought these tRFs and miRs in the MCAo, middle cerebral artery occlusion mouse model of stroke. The levels of several patients-modified cholinergic-targeted tRFs and miRs were also modified in MCAo mice, supporting their causal role in post-stroke recovery. Examples include 3’-fragments derived from two different leucine tRNAs, LeuAAG/LeuTAG, both predicted to target the inflammation-blocking nicotinic acetylcholine receptor alpha7 (CHRNA7), which were upregulated both in blood samples of stroke patients and in MCAo mice (1.13 log2 fold change in patients, p = 0.0018 and 4-fold increase in MCAo vs. naïve animals, p <0.001). Interestingly, these tRFs show high sequence similarity to the previously described miR-1260, predicted to target CHRNA7, indicating the potential role of post-stroke modified circulation miRs and tRFs in regulating cholinergic gene expression. Our results highlight cholinergic-targeted and inflammation controlling tRF and miR changes in post-stroke recovery, indicating that these small RNAs may serve as brain-to-body messages assisting post-damage recovery. In-depth functional investigations of those tRFs in cultured cells of human origin are underway.

Advisor: Prof. Hermona Soreq
Population dynamics and entrainment of basal ganglia pacemakers are shaped by their dendritic arbors

Lior Tiroshi

The theory of phase oscillators is an essential tool for understanding population dynamics of pacemaking neurons. GABAergic pacemakers in the substantia nigra pars reticulata (SNr), a main basal ganglia (BG) output nucleus, receive inputs from the direct and indirect pathways at distal and proximal regions of their dendritic arbors, respectively. We combine theory, optogenetic stimulation and electrophysiological experiments in acute brain slices to ask how dendritic properties impact the propensity of the various inputs, arriving at different locations along the dendrite, to recruit or entrain SNr pacemakers.

By combining cable theory with sinusoidally-modulated optogenetic activation of either proximal somatodendritic regions or the entire somatodendritic arbor of SNr neurons, we construct an analytical model that accurately fits the empirically measured somatic current response to inputs arising from illuminating the soma and various portions of the dendritic field. We show that the extent of the dendritic tree that is illuminated generates measurable and systematic differences in the pacemaker’s phase response curve (PRC), causing a shift in its peak. Finally we show that the divergent PRCs correctly predict differences in two major features of the collective dynamics of SNr neurons: the fidelity of population responses to sudden step-like changes in inputs; and the phase latency at which SNr neurons are entrained by rhythmic stimulation, which can occur in the BG under both physiological and pathophysiological conditions.

Our novel method generates measurable and physiologically meaningful spatial effects, and provides the first empirical demonstration of how the collective responses of SNr pacemakers are determined by the transmission properties of their dendrites.

Advisor: Dr. Joshua A. Goldberg
Specific contribution of PV neurons to motor timing in behaving primates

Abdulraheem Nashef

At movement onset, motor cortical activity undergoes a large increase in activity, that is often directionally tuned. This change in neural activity provides the main driving force for downstream motor machinery and is responsible for producing well timed motor action. It is commonly accepted that the cerebellum plays an important role in producing this volley of activity, the exact way cerebellar signals interact with motor cortical circuitry are yet unclear.

Previously we have shown that motor cortical response to activation of the cerebellar-thalamo-cortical (CTC) pathway is dominated by inhibition, and that this inhibition is independent of the early excitatory response. The aims of this work was to further investigate the mechanisms through which the observed inhibition is mediated and its specific contribution to timing of motor actions. To address this question we implanted two monkeys with a chronic stimulating electrode at the superior cerebellar peduncle (SCP) which allowed an efficient activation of the CTC pathway. We took advantage of two well documented findings: first, thalamocortical (TC) fibers make contact with pyramidal neurons and PV interneurons. Second, the synaptic contact between TC fibers and PV cells can be blocked selectively by a specific drug (NASPM). We recorded neural activity from motor cortex using a custom-made multi-barrel pipette that allowed extracellular recording of cortical activity while applying NASPM. We tested for modulation in cell response to NASPM application in order to classify cells into excitatory (pyramidal) or inhibitory (PV) cells. We found that, similar to sensory areas, motor cortical areas integrate thalamic input via a feed-forward inhibition circuit. We further found that FS interneurons in motor cortex fired at higher rates than pyramidal neurons ($N_{FS} = 6, N_{Pyr} = 21; \text{mean}_{FS} = 25.8 \text{ Hz}, \text{mean}_{Pyr} = 14 \text{ Hz}; \text{two-samples t-test, } p<0.02$), yet the width of tuning curve was similar across cell types. Finally, we found that at movement onset FS neurons were recruited earlier and fired higher than Pyr neurons (peak gain- FS: 28.4 Hz, Pyr: 9.9 Hz, t-test, $p=0.005$). This seemingly counterintuitive sequence of events may be responsible for the transient synchronized firing at movement onset which is needed to efficiently recruit downstream elements. It may further enhance signal-to-noise ratio by suppressing irrelevant input and emphasizing the excitatory volley from the TC system which occur just in time to overcome the inhibitory signal.

Advisor: Prof. Yifat Prut
Attention related coordination of cortical state within and between areas V1 and V4 of the Macaque

Alexander Thiele, Newcastle University, UK

Cortical activity reveals spontaneous activity fluctuations that are not solely determined by external inputs, but reflect changes to the underlying excitability of neurons, referred to as cortical state. Cortical states fluctuate strongly between sleep-wake states, but even during wakefulness state fluctuations do occur, which influence sensory processing as well as behavioural performance. The talk will delineate how cortical state changes manifest as changes in coordinated neuronal firing, and as coordinated changes of oscillatory activity changes across cortical layers within and between cortical areas V1 and V4, and how these are affected by spatial attention.