NGN Meeting 2017

Abstracts

Indian Institute of Science Education and Research,
Pune, India

Contents

1 Talks

1.1 Ali Asgar Bohra

Neuronal circuit for bitter taste processing in Drosophila

In Drosophila, gustation is important for feeding, avoiding of toxic substances, recognizing mates and finding appropriate locations for egg laying. The neural circuits, which process gustatory information in the central nervous system of flies, are poorly characterized. We are studying second order neurons which process information from sensory neurons for eliciting appropriate behavior. For this we have used a library of enhancer-Gal4 lines in behavioral gustatory screening. In this screen we have found numerous interneurons whose activation via targeted TrpA1 expression results in deficits in the proboscis extension/retention response to natural gustatory stimuli. Among these interneurons we have identified a pair of sub esophageal cells, which receive input from bitter sensitive sensory neurons. Targeted activation of these interneurons by TrpA1 causes abnormal responses to appetitive stimuli such as sugar and water. Further analysis of the structure and function of these identified interneurons indicates that they play an important role in bitter taste perception and in the resulting inhibition of proboscis extension and feeding. The genetic identification of these interneurons now makes it possible to search for other interneurons that are synaptically interconnected and make up the circuitry for bitter taste perception and aversion response.

1.2 Aridni Shah

Egr-1, a molecular player involved in time related learning and memory in honey bees?

Honey bees have been a successful model system to study diverse learning and memory processes under free flying conditions and in restrained lab assays. They have been shown to possess astonishing cognitive capabilities like learning time, colour, odour, location etc. of the food source. Since, foragers can be trained to forage at an artificial feeder, we used the foraging behaviour to identify specific molecular processes involved in learning and memory in a natural context.

Honey bee foragers were time-trained to an artificial feeder for several days in an outdoor flight cage and collections were made at different time points as per the experimental requirement. The RNA levels of different genes were measured using qPCR.

Honeybees foraging at an already known feeder showed a long lasting up-regulation of three immediate early genes (Egr-1, Hr38, kakusei) and also an up-regulation of candidate downstream genes involved in dopamine ecdysone signalling pathway (EcR,Ddc, DopEcR). Also, Egr-1 mRNA levels were significantly up-regulated at the time of feeder training compared to time points before and after feeder training, when the feeder was not presented. Based on this finding, we hypothesized that the Egr-1 expression might be under the regulations of the circadian clock. To test this, we prevented the time-trained foragers from leaving the hive using the artificial rain paradigm. In these experiments, we also observed a significant but lower up-regulation of Egr-1 around the time of feeder training. Together our results indicate two different genomic responses occurring during daily foraging: (a) continuous daily foraging induces a genomic response mediated by immediate early genes like Egr-1, Hr38 and kakusei. This genomic response can be involved in learning and memory processes as well as cellular homeostasis; and (b) time-training results in an anticipatory up-regulation of Egr-1and hence could be a molecular player involved in time-related memory processes.

1.3 Joby Joseph

A network motif that does fine tuning of a negative feedback in a memory center

Shilpi Singh and Joby Joseph

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The mushroom body (MB) in the insect olfactory circuit is known to be the higher center for processing olfactory information and has been shown to play important role in learning and memory. The intrinsic neurons of MB are Kenyon cells (KCs) and it feed forwards its sparse output in response to odor stimuli onto an inhibitory neuron called the giant GABAergic neuron (GGN) in the output lobe called alpha lobe. The GGN which is GABAergic feeds it back onto the MB calyx. It has also been found that the GGN has reciprocal inhibitory connections with a neuron called the IG (Inhibitor of GGN). It is not known what properties (anatomical or physiological) or functions the IG plays in this circuit. With this end in mind, we recorded intracellularly from GGN and developed a method to detect IG spikes from the IPSP in GGN membrane potential. We derive the properties of IG using this method and show that IG is responsive to odor and receive input from olfactory pathway downstream of KCs. IG responds even when there is no depolarization in GGN consistent with quick response in IG compared to GGN. KC to IG pathway show pair pulse facilitation similar to KC to GGN synapse. The lateral horn (LH) interneurons are inhibited by KC stimulation suggesting that GGN arborization in LH is and output of GGN.

1.4 Bhaktee Dongaonkar

Effects of unipolar and bipolar depression in episodic memory updating

Background: When a consolidated episodic memory is reactivated, it becomes modifiable and can be updated or integrated with new learning. This memory updating paradigm has been increasingly explored for behavioral treatments of stress and anxiety disorders such as PTSD. However, most of anxiety disorders are accompanied by depressive symptoms. How reliably patients in a depressive state can update memories is relatively less understood. We, therefore, decided to explore effects of depression on episodic memory updating.

Methods: Unipolar or bipolar depression patients and age/education matched individuals controls were included. Participants learned a List 1 of 20 everyday objects on Day 1. On Day 3, some participants were reminded of their experience from Day 1 before everybody learned List 2 of 20 different everyday objects. The unipolar, bipolar, and control groups were therefore randomly split into 'reminder' or 'no-reminder' conditions. On Day 5, all participants were instructed to recall objects from Day 1 (Exp 1) or Day 2 (Exp 2). List 1 was considered updated when List 2 items were incorporated into List 1 items, contingent upon reactivation of List 1 memory.

Results: In Experiment 1, despite impaired List 1 recall in all patient groups, the ability to update in unipolar and bipolar reminder groups was proportional to the control reminder group, suggesting intact ability to update. Unexpectedly, bipolar no-reminder group also showed updating, overriding the need for reactivation before reconsolidation. In Experiment 2, the impaired recall (List 2) persisted in all patient groups. Additionally, both bipolar reminder and no-reminder groups updated List 2, confirming that bipolar patients updated List 1 and List 2 independent of reactivation, or bidirectional updating. The unipolar and control groups update only List 1, when reactivated, suggestive of unidirectional updating.

Conclusions: Our results suggest that behavioral treatments in anxiety disorders with underlying depression may be successful in patients with symptoms of unipolar depression. In anxiety disorders with bipolar depression, the same behavioral treatments might turn out to be ineffective.

1.5 Kavita Babu

The C. elegans ortholog of mammalian Calsyntenins, CASY-1, functions at the Neuromuscular Junction

The C. elegans ortholog of mammalian Calsyntenins, CASY-1, is an evolutionarily conserved type-I transmembrane protein that is highly enriched in the nervous system. Mammalian calsyntenins are strongly expressed at inhibitory synapses, but their role in synapse development and function is still elusive. Here, we report a crucial role for CASY-1/Calsyntenin isoforms in regulating GABAergic synaptic transmission at the C. elegans neuromuscular junction (NMJ). The shorter isoforms of CASY-1; CASY-1b and CASY-1c, express and function in GABA motor neurons where they regulate GABA neurotransmission. Using pharmacological, behavioral, electrophysiological, optogenetic and imaging approaches we establish that GABA release is compromised at the casy-1 NMJs. Further, we demonstrate that Calsyntenin/CASY-1 is required to modulate the trafficking of GABA synaptic vesicle (SV) precursors through a possible interaction with the SV motor protein, KIF1A/UNC-104. This study proposes a possible evolutionarily conserved model for the regulation of GABA synaptic functioning by mammalian Calsyntenins. Deregulation of the mammalian Calsyntenins is thought to be coupled with age-related-conditions like Alzheimer's and Parkinson's disease, hence future investigations using C. elegans casy-1 model could provide a deeper understanding of the pathology of these disorders.

1.6 Madhumala K Sadanandappa

Circuit plasticity and inhibitory engrams in behavioral habituation

Habituation allows an organism to ignore familiar percepts and thereby, enables the organism to more efficiently and selectively respond to salient features of its surrounding environment. Habituation is ubiquitous and important for normal cognitive and emotional systems. However, how it occurs remained unclear.

In a relatively well-defined neural circuit of Drosophila olfactory system, we have addressed the underlying mechanisms of habituation in terms of neuronal, molecular and circuit involved. Strong aversive responses to odorants are dramatically reduced if flies are previously exposed to these odors. Brief odor stimulation induces short-term habituation (STH), which lasts for tens of minutes, whereas prolonged odorant exposure results in long-term habituation (LTH) that recovers in days. Behavioral studies combined with genetics, anatomical and live-imaging approaches suggest that synapse-specific potentiation of GABA release from the antennal lobe local interneurons (LN) onto odorant-selective projection neurons (PN) drives both forms of habituation. Most strikingly, STH depends on facilitation of GABA release from LNs that is promoted by cyclic-AMP, CaMKII and synapsin. On contrary, LTH is associated with an odor- selective growth of new stable LN-PN synapses through mechanisms that require new gene expression. Together, these discoveries lead us to propose a general model for inhibitory potentiation that drives habituation in different sensory circuits across species. In gist, through application of a simple inhibitory synaptic learning rule, neural systems create inhibitory engrams that precisely match and cancel excitatory patterns triggered by familiar percepts. This model for habituation and its implications will be discussed.

1.7 Megha

Identification of intracellular Ca2+ signalling mediated neuropeptidergic regulation of development under nutritional stress in Drosophila melanogaster

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Nutrition is of the primary determinants of animal size and development. Under poor nutritional conditions, both growth and maturation have to be optimised in order to give rise to a fully functional adult. Neuropeptides (NPs) are a class of neuromodulatory molecules produced in neurons, that can either locally or systemically regulate animal response to external cues. Reasoning that neuropeptides may therefore play a role in coupling animal development to nutritional cues, D. melanogaster (Dmel) larval to pupal transition under late-stage protein deprivation was used as a model to identify such NPs. There are ¿40 neuropeptides annotated in Dmel; this study focused on those regulated by intracellular Ca2+ signalling mediated by the inositol 1,4,5 trisphosphate receptor (IP3R), an ER Ca2+ channel and STromal Interacting Molecule (STIM), a regulator of Store-operated Ca2+ entry (SOCE). Genetic studies revealed a role for a pair of 2 bilateral peptidergic neurons, secreting short Neuropeptide F (sNPF) and corazonin, in supporting pupariation under nutritional stress. How intracellular Ca2+ signalling may regulate the two neuropeptides - at the level of protein transcription, translation or release is being investigated. Both IP3R and STIM have well-known roles in elevating ligand-induTalkced cytosolic Ca2+ levels and how this mechanism, particularly in neurons, where depolarisation also leads to elevated cytosolic Ca2+ levels, regulates neuronal output, is an outstanding question. The identified sNPF and Corazonin-positive neurons provide the means to answer this question, in a specific physiological context viz., pupariation under nutritional deprivation.

1.8 Minal Jaggar

Chronic electroconvulsive seizure (ECS) treatment enhances neuronal plasticity in the hippocampus in an age-dependent fashion

Electroconvulsive seizure (ECS) therapy, discovered in 1930s, is a robust antidepressant therapy prescribed especially in cases of geriatric depression and treatment resistance to pharmacological antidepressants. While several hypotheses involving enhanced neurogenesis, neurotrophic factors, synaptic plasticity, and monoamine modulations have been proposed, the basis of its functioning remains poorly understood. Though ECS is a treatment of choice for elderly population, most preclinical literature on ECS has been carried out in post-pubertal adult (2-4 month old) animals and often extrapolated for older animals.

In this study, we have systematically analyzed chronic ECS evoked behavioral, cellular, morphological, and gene expression profiles in an emotionally relevant circuit, the hippocampus of young adult (3 month) and middle aged (12 month) male rats. ECS reduced immobility time on the forced swim test, increased hippocampal expression of several immediate early genes, matrix metalloproteases and neurotrophic factors, neurogenesis with robust increase in quiescent neural progenitor population, and enhanced hippocampal synaptic plasticity across both the ages. ECS reduced the number of perineuronal nets (PNN) with drastic reduction of parvalbumin+-PNN+ neurons in various hippocampal subfields across both the ages. Strikingly, reelin positive cells in the hippocampal subfield were reduced in 3 month- but not 12 month- old rats post chronic ECS treatment. Our results support the enhanced plasticity hypothesis of antidepressant action and paves way for further research on effects of ECS on perineuronal nets, interneurons and reelin signaling.

1.9 Nishan Shettigar

Hierarchies in light sensing and neural processing revealed through regeneration

Light sensing has independently evolved multiple times under diverse selective pressures but has been examined only in a handful among the millions of light-responsive organisms. Unsurprisingly, mechanistic insights into how differential light processing can cause distinct behavioral outputs are limited. We have shown that planarian flatworms (Schmidtea mediterranea) can perform complex processing using their simple eyes. Although planarian flatworms lack wavelength-specific eye photoreceptors, a 25 nm change in light wavelength is sufficient to completely switch their phototactic behavior. We show that planarians are sensitive to the amount of light absorbed at the eye, and are then able to convert these 'effective light intensity changes into clear behavioral outputs. Using planarians remarkable ability to regenerate, we have shown that this acute light intensity sensing and processing are layered on simple light detection. Unlike intact worms, partially regenerated animals with eyes can sense light but cannot sense finer gradients. We have also designed new methods visualize the changes in the eye and neural networks. Imaging studies have shown a marked increase in planarian brain synaptic density over the course of regeneration. Also, there is a clear increase in the number of eye photoreceptor cells and commensurate enhancement and patterning of the rhabdomeric structures. These methods for imaging a regenerating visual network offer a great platform to screen for new molecules that regulate eye growth, patterning and function. Planarians also show a "reflex-like," eye-independent (extraocular/whole-body) response to low ultraviolet A light, apart from the "processive" eye-brain–mediated (ocular) response. Competition experiments between ocular and extraocular sensory systems reveal dynamic interchanging hierarchies. In intact worms, cerebral ocular response can override the reflex-like extraocular response. However, injury-regeneration again offers a time window wherein both responses coexist, but the dominance of the ocular response is reversed. Our experiments suggest the extraocular light-sensor is a novel opsin protein expressed all over the planarian body. Planarians with two distinct light sensing modalities provide us with exciting opportunities to study interaction and dynamics between them. Overall, our work shows novel light sensing and processing in flatworms, and provides new insights into eye and brain regeneration and patterning.

1.10 Nixon Abraham

Olfactory decisions: behaviour to neural circuits, a reverse approach

Decisive or non-decisive behaviours happen as a result of the interactions between different neuronal circuits in our brain. What is the best approach to dissect out the neuronal circuits responsible for specific behaviours? At IISER Pune, our lab studies the mechanisms of olfactory decision-making by using mouse model and combine the state-of-art automated behavioural training, electrophysiology and optogenetics.

Olfaction was traditionally thought as a 'slow' sense compared to other senses. By doing highly precise olfactory behavioural experiments we have proved this concept wrong. Our results show that mice can discriminate simple odors in ≈200 ms and complex binary mixtures with additional tens of milliseconds1. We are able to modify the functions of specific circuits in the olfactory bulb2 by using modern techniques such as optogenetics and chemogenetics and thereby modulate olfactory learning in a bidirectional way3. Our recent behavioural experiments prove the importance of stimulus duration in controlling the olfactory learning and memory. After getting a stable phenotype, we are now aiming to go back and dissect out the mechanisms responsible for this phenomenon. As specific behaviours provide the ultimate readouts from our brain, it may be better to target specific neuronal circuits after observing a clear behavioural phenotype.

1. Abraham, N. M. et al. Maintaining accuracy at the expense of speed: stimulus similarity defines odor discrimination time in mice. Neuron 44, 865-876, doi:S0896627304007536 [pii] 10.1016/j.neuron.2004.11.017 (2004).

2. Abraham, N. M. et al. Synaptic inhibition in the olfactory bulb accelerates odor discrimination in mice. Neuron 65, 399-411, doi:S0896-6273(10)00014-0 [pii] 10.1016/j.neuron .2010.01.009 (2010).

3. Gschwend, O. et al. Neuronal pattern separation in the olfactory bulb improves odor discrimination learning. Nat Neurosci 18, 1474-1482, doi:10.1038/nn.4089 (2015).

1.11 Rajesh Vinnakota

Modulation of AMPA and Kainate Receptor Functions by their Auxiliary Subunits

Ionotropic glutamate receptors (iGluR) are ligand-gated ion channels that transduce chemical signals into electrical ones leading to communication and information transfer in central nervous system in the form of action potentials (APs). Playing key roles in fundamental process, these receptors are implicated in numerous neuronal disorders. The understanding of functional properties of these ion channels and their modulation via interacting auxiliary subunits is the key to designing novel therapeutic interventions targeting these receptor complexes. GluK2 and GluA2 are receptors belonging to AMPA and Kainate receptor family respectively with distinct functional properties. We have undertaken analysis of trafficking and modulation of biophysical properties of these AMPA and Kainate receptors by their auxiliary subunits Neto1 (neuropilin and tolloid-like proteins) and CKAMP44 (cysteine-knot AMPAR modulating protein) respectively. In the present study, 14 chimeric receptors were designed by swapping the amino terminal domain (ATD), Ligand binding domain (LBD) and transmembrane domain's (TMD) between GluK2 and GluA2 receptor subunits. Surface expression along with functionality of the chimeras was verified via biotinylation and electrophysiological assays respectively. In order to dissect out the domains responsible for interaction between CKAMP44 and GluA2, we carried out electrophysiological assays for wildtype and various receptor chimaeras co-expressed with CKAMP44. CKAMP44 slows down the recovery from desensitization state in native GluA2 receptors. Interestingly, our results show that the ATD domain seems to be important for interaction with CKAMP44 as swapping it with that of GluK2 in one of our designed chimeric receptor leads to significantly slower rates of both deactivation and desensitization whereas, the rate of recovery from the desensitized state is enhanced. Similarly, swapping GluA2 LBD with GluK2 LBD domain increases the rates of deactivation, desensitization and current rise times. Our results provide novel insights into how iGluRs are modulated by their auxiliary proteins and pave the way towards designing new therapeutic interventions targeting AMPA and Kainate receptors for various neurological disorders.

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1.12 Rishikesh Narayanan

Degeneracy in the hippocampal formation

Degeneracy, the ability of disparate constituent elements to yield analogous function, is a ubiquitous phenomenon that imparts robustness to biological processes across different scales spanning gene interactions to behavioral repertoires. Here, a case will be built for the existence of such degeneracy in the cellular and network physiology of neurons in the rodent hippocampal formation, a brain region that plays critical roles in spatial learning and episodic memory. This case will be built on several lines of computational and electrophysiological evidence that spans the hippocampal formation, covering the entorhinal cortex, the dentate gyrus and the CA1 subfield of the hippocampus. Conceptually, brief descriptions of lines of evidence for the expression of degeneracy in single-neuron electrophysiology, intraneuronal functional maps, synaptic localization required for sharp-tuning of hippocampal place fields, efficient phase coding, short- and long-term synaptic plasticity profiles and network-scale response decorrelation will be presented.

1.13 Sahil Moza

Precise balance controls gain and timing in the hippocampus

Excitation and Inhibition are known to be balanced in many brain circuits, leading to clamped excitability and gain control. However, the granularity of this balance is not well established. Are stimuli balanced on average (loose balance) or are arbitrary combinations of presynaptic input balanced (detailed balance)? We stimulated hippocampal CA3 neurons with hundreds of combinations of optical stimuli, and monitored CA1 neuron responses in mouse brain slices. We observed that inhibition followed excitation at millisecond timescales, and was tightly proportional to excitation for all stimulus combinations, demonstrating detailed balance at the hippocampal CA3-CA1 system. We then asked how this tightly balanced feedforward inhibition integrates with excitation at the CA1 neurons. Surprisingly, we found that integration of E and I leads to a non-linear sum at the CA1 neuron, with progressively smaller increments in the summed output with increasing input. This subthreshold gain control mechanism, that we call Subthreshold Divisive Normalization (SDN), emerges as the inhibitory onset advances toward excitatory onset with increasing input strength. Lastly, SDN helps to split the information about the input strength between PSP amplitude and PSP timing, thus helping decouple spiking probability from spike timing.

1.14 Sandhya Koushika

Cargo crowding at actin-rich regions along axons causes local traffic jams in neurons that maybe overcome by DLK dependent reversals

Steady axonal cargo flow is central to the functioning of healthy neurons. However, a substantial fraction of cargo in axons remains stationary across a broad distribution of times. We examine the transport of precursors of synaptic vesicles (pre-SVs), endosomes and mitochondria in C. elegans touch receptor neurons, showing that stalled cargo are predominantly present at actin-rich regions along the neuronal process. Cargo stalled at actin-rich regions increase the propensity of moving cargo to stall at the same location, resulting in traffic jams. Such local traffic jams at actin-rich regions are likely to be a general feature of axonal transport since they occur in Drosophila neurons as well.

Repeated touch stimulation of C. elegans reduces the density of stalled pre-SVs, indicating that these traffic jams can act as both sources and sinks of vesicles. This suggests that vesicles trapped in actin-rich regions are functional reservoirs that may contribute to maintaining robust cargo flow in the neuron. We also see that pre-SVs reverse predominantly at regions where cargo are stalled in a DLK (Dual Leucine Zipper Kinase) dependent manner. Our simulations show that reversals are a key element that allows steady cargo transport.

1.15 Sourav Banerjee

No longer junk: non-coding RNA centric mechanisms of synaptic plasticity

The complex interplay between synaptic activation and quiescence is crucial for neural circuits to govern various cognitive functions and protect neural circuits from the influence of fluctuating external stimuli to maintain homeostatic brain functions. Although, distinct mechanisms operating at the systems level have been shown to modulate these two critical phases (i.e. excitability and quiescence) of the synapse, understanding of the molecular interplay that govern these two dynamic states of synapse remain poorly understood. Our whole-cell patch clamp recording revealed that the bicucullin-induced alteration of basal network activity of hippocampal neuron was tuned back to its homeostatic threshold point after co-application of both protein synthesis and degradation inhibitors, suggesting a combinatorial control of protein synthesis and degradation in maintenance of homeostatic network function. We observed that component of the core proteasome machinery is co-sedimented with protein synthesis machinery and directly interact with each other. Furthermore, we have demonstrated that bicucullin regulates the composition of microRNA (miRNA) containing RNA inducing silencing complex through a combinatorial control of protein synthesis and degradation for maintenance of set point of homeostatic synaptic balance.

In another study, we have investigated a how external stimulus modulates rapid remodeling of synapses de novo via localized protein synthesis to make long-term adaptive changes in the neuronal circuitry. Using various biochemical and phtoconvertible reporter based assay, we have demonstrated that the neuronal activity induces selective degradation of miRNAs at the hippocampal synapses. This degradative control of miRNAs resulting in localized protein synthesis at the synapse for its functional remodeling. Taken together, our studies are enumerating a RNA centric mechanism of activity induced adaptive changes of neuronal network and their homeostatic function.

1.16 Souvik Modi

A Quantum Dot conjugated nanobody for imaging receptor dynamics at synapses in vitro and ex vivo

Neurons communicate with each other through synapses, which show enrichment for specialized receptors. Although many studies have explored spatial enrichment and diffusion of these receptors in dissociated neurons using single particle tracking, very little is known about their dynamic properties at synapses in complex tissue like brain slices. Here we report a small and highly specific Quantum Dot conjugated nanoprobe functionalized with a recombinant single domain antibody fragment (VHH fragment) against a green fluorescent protein that provides information on the diffusion of adhesion molecules on growth cones and neurotransmitter receptors at synapses. Our data reveal that this smaller probe can easily access both excitatory and inhibitory synapses and measure neurotransmitter receptor dynamics in hippocampal cultures as well as in ex vivo rat brain slices. This method provides an approach for research in cell biology that requires labelling of any GFP tagged membrane protein and allows the study of their clustering, diffusion, and transport in vitro as well as more similar to in vivo environments such as brain slices.

1.17 Sthitapranjya Pati

Early adversity and development of psychopathology

Early life stress is associated with enhanced susceptibility to adult psychopathology. Diverse early life animal models ranging from the early stress of maternal separation to pharmacological elevation of serotonin levels in postnatal life, as well as maternal immune activation, impinge on the 5-HT2A receptor, regulating receptor function and expression, in particular within the prefrontal cortex. Further, pharmacological blockade of the 5-HT2A receptor overlapping with the specific early life perturbations has been shown to prevent the emergence of anxiety and depressive behavior in adulthood. In contrast, stimulation of the 5-HT2A receptor during postnatal life is sufficient to evoke changes in mood-related behavior in adulthood. Using DREADD based pharmacogenetic approaches to evoke excitation in CAMKII-positive excitatory neurons in cortical circuits we show that transient DREADD-based stimulation in postnatal life is sufficient to enhance anxiety and depressive behavior well into adulthood. DREADD Gq activation from P2-P14 also evokes enhanced schizophrenia-like behavior with deficits in prepulse inhibition. DREADD activation during this temporal window does not influence cognitive or social behavior. Experiments are currently underway to test the influence of early adversity in 5-HT2A receptor knockout mouse models.

1.18 Supriya Ray

A Novel Behavioral Parameter for Estimation of Stopping Efficacy

Countermanding paradigm is often considered to investigate executive control in goal-directed behaviour. Race model of countermanding assumes a competition between a reactive (go) and an inhibitory (stop) process both ramping up to reach a threshold at stochastic rate. The model provides a means to estimate how much time an individual might take to stop a pre-planned movement. This behavioural parameter is known as the stop signal reaction time (SSRT). The estimation of SSRT is not only sensitive to the reaction time distribution and stopping performance, it also relies upon several assumptions that do not have known physiological foundations. We recorded eye-movements of healthy human adults. In each trial, a number flashed at the centre that instructed participants to orient their gaze to one of two squares placed at the left and right to the centre. However, in a small proportion of trials, after a variable delay, called stop-signal delay (SSD), a letter 'X' appeared briefly at the centre that instructed participants to maintain gaze at the centre. Our data indicate violation of predictions by race model. In line with an alternative model that postulates that the speed of motor planning is decreased following the stop-signal onset, we introduce a novel behavioral parameter to estimate stopping efficacy in the oculomotor domain. We demonstrate that non-cancelled RT can be approximated by an exponential function of parallel processing time or PPT (i.e., the delay between the stop-signal and saccade onset) of the form RT = aeb(PPT)+c. We estimated the average time spent holding the gaze before the stop-signal onset by calculating non-cancelled RT at PPT = 0, from the sum of the fitting coefficients a and c. This behavioural parameter, which we will refer to as the peri-signal fixation time (PSFT), was found negatively correlated with error in inhibition. In other words, the longer the gaze was withheld the higher the probability of cancelling a saccade. We argue that PSFT is a better measurement than SSRT to estimate the ability to withhold a saccade, and emphasizes the progress in planning saccade at the time of onset of the stop-signal is critical for countermanding.

1.19 Venkatakrishnan Ramaswamy

An Algorithmic Barrier to Neural Circuit Interrogation

Neuroscience is witnessing impressive technical progress in techniques for interrogating neural circuits. This progress includes optical readout of neural activity, capability to optogenetically stimulate/silence subsets of neurons in-vivo, in awake behaving animals, and ascertaining exact connectivity, for increasingly larger neural circuits. It is generally assumed that scaling up of these technologies will be sufficient for us to understand mechanistic computation in neural circuits that lead to behavior. Arriving at such an understanding will require efficient algorithms for neural circuit interrogation. The algorithms will seek to prescribe the smallest number of experiments necessary (say as a function of the number of neurons in the network), wherein each experiment might involve circuit manipulations and concurrently imaging activity, while attempting to elicit behavior. Theoretical Computer Science has known, from over half a century of work, that some problems have fast algorithms whereas certain others require intractably many steps of computation to solve, in general. It is as yet unclear in which class of problems those pertaining to neural circuit understanding fall in.

Here, using techniques from Computational Complexity Theory, it is proved, mathematically, that establishing any reasonable notion of full falsifiable understanding of mechanistic computation in neural circuits for a fixed behavior is NP-hard, even if the exact circuit structure is known. This is to say that no general algorithm exists to solve this class of problems that always uses sub-exponential number of experiments in the number of neurons, unless the complexity class P=NP. If, remarkably, P=NP were true, it would imply that hundreds of problems — many of them commercially important and extensively studied for decades — would have sub-exponential algorithms, where none have been found to date. Indeed, the P=NP? question is one of the outstanding open problems in Mathematics of our time and the answer is widely believed to be in the negative.

This result implies a strong (and hitherto unexpected) algorithmic barrier to understanding mechanistic computation in neuronal networks and suggests that algorithmic intractability might pose a fundamental roadblock in understanding the brain.

1.20 Vidur Sabharwal

JIP3/UNC-16 inhibits the function of regeneration promoting isoform of DLK-1.

Neurons in the adult nervous system have a limited ability to regenerate after injury. The extent of neuronal regeneration after injury depends on the intrinsic growth potential of neurons and their extracellular environment, both influenced by several genes. We show that UNC-16 plays an inhibitory role during the early stages of neuronal regeneration after axotomy. UNC-16, a C. elegans JIP3 (JNK Interacting Protein 3) homologue, belongs to a family of classical scaffolding molecules known to be able to switch their roles from growth promoting to inhibitory based on their levels and time of activation or deactivation. We also show UNC-16's inhibitory role is dependent on Dual Leucine Zipper Kinase-1 (DLK-1). DLK-1 is an essential MAPKKK for neuronal regeneration and has been reported to interact with JIP3. DLK-1 has two isomers, long and short, of these, DLK-1 long promotes regeneration while DLK-1 short inhibits regeneration. We show that UNC-16 inhibits the regeneration promoting activity of DLK-1 long but does not influence the activity of DLK-1 short. We find that UNC-16 promotes the DLK-1 long punctate localization in a concentration dependent manner limiting its availability at the cut site. We also show that UNC-16 levels are responsible for negatively regulating microtubule dynamics at the cut site immediately after axotomy. However increased MT dynamics alone is insufficient to explain increased regeneration. UNC-16 also restricts filopodial outgrowths in a DLK-1 dependent manner which, along with MT dynamics, may contribute to the observed faster rate of neuronal regrowth in unc-16 animals.

We suggest a model where UNC-16 may hold DLK-1 long in a complex and restrict the availability of active DLK-1 long and thereby inhibit regeneration. The dual inhibitory control by both UNC-16 and DLK-1 short can calibrate the intrinsic growth promoting function of DLK-1 long in vivo. We thus show that JIP3 could play its inhibitory role to allow tight temporal and spatial control of DLK-1 function.

1.21 Yogesh Dahiya

CREB-1 and associative learning in Caenorhabditis elegans

Memory formation is crucial for the survival of animals. The process of memory formation is largely conserved across animal species at the cellular and molecular level. One such conserved molecule is CREB-1, a transcription factor that can be activated in the neurons in an activity dependent manner. In order to study aspects of learning and memory formation (LTM), we have developed olfaction based assays to test LTM formation in C. elegans. Using these assays we have found LTM defects in the crh-1 mutant worm, which codes for the C. elegans homolog of the mammalian creb-1 gene. Our experiments show that out of the six CRH-1 isoforms in C. elegans, two specific isoforms, CRH-1c and CRH-1e, can rescue all the associative learning and memory defects in the mutant animals. CRISPR based CRH-1c and CRH-1e deletion mutants show memory deficit comparable to crh-1 deletion mutants thus establishing the memory related functions of these isoforms. Further, by temporally regulating the expression of the CRH-1 transcription factor using a heat shock promoter we demonstrate that CRH-1 is required for acquisition/consolidation phase of memory formation. We could completely rescue the learning defect of crh-1 animals by expressing CRH-1c, CRH-1e in a small subset of 11 neurons under the control of nmr-1 promoter.

2 Posters

2.1 Aditya Asopa

A Study on Role of Single Neurons as Detectors of Upstream Sequential Network Activity in Hippocampus – System Development

Hippocampus in many ways is a cognitive centre of the brain. It is shown to be a site of processes as diverse as episodic memory, spatial and temporal mapping of the world, short term memory formation and so on. There are many observations of ordered activity in the its networks. Very recently, our lab has put forth a hypothesis that the chemical networks inside a single pyramidal neuron can enable the neuron to respond to a particular order of inputs compared to other orders imparting the capacity to essentially detect sequential activity in upstream networks. This becomes very important in regions like hippocampus because its above-mentioned role in information processing. To test this hypothesis, we have built an optogenetics-electrophysiology system which can generate a spatio-temporal pattern of inputs along the dendrites of a neuron. At a resolution of 1 micron at 1000 frames-per-second, this system can generate optical patterns in channelrhodopsin expressing hippocampal sections, which can be translated into input patterns on a target cell. We have characterized the optical activation of patched hippocampal pyramidal neurons using the system. The results of the system-characterization also trace out the optical receptive field of an optically excitable neurons.

2.2 Amruta Vasudevan

Investigating mechanisms governing cargo transport at neuronal branch points

Across vertebrate and invertebrate systems, it is observed that neurons exhibit complex cellular morphologies by extending processes that form branches. However, little is known about whether pre-SVs tend to distribute randomly across all branches or exhibit a preference toward certain branches over others. We address this question using the Posterior Lateral Microtubule (PLM) cells of the model organism C. elegans. Using live imaging, we examined transport of pre-SVs in the PLM process at the branch point using multiple markers specific for pre-SVs. We observed that ∼50% of anterogradely moving pre-SVs enter the collateral branch, while only ∼15% go straight along the main process. UNC-104/Kinesin- 3 is the primary motor necessary for anterograde transport of pre-SVs in PLM neuron. We observed that in reduced levels of UNC-104, vesicles tend to predominantly pause at the branch point (∼80%) and show reduced turning behaviour (∼15%). We further observed that pre-SVs in mutants of proteins important for cargo-motor processivity, viz., SAM-4 and SYD-2/Liprin-α similarly show reduced turning at the branch point. Further, mutations in specific domains of UNC-104 are known to affect motion properties of the cargo-motor complex in vivo. We are investigating how these mutants affect the ability of the cargo-motor complex to traverse the PLM branch point. Loss of function mutation in dhc-1 (subunit of the Dynein motor complex) reduces turning behaviour of pre-SVs to ∼15%. This suggests that a balance between anterograde and retrograde motors is necessary for preferential turning. We are investigating how a reduction in levels of both motors together influence preferential turning. Regions of collateral branching have been shown to have microtubule intersections in mammalian neurons in culture. At microtubule intersections, cargo has been shown to switch between microtubule tracks both in vitro and in vivo. It is possible that this layout influences the behaviour of the motor-cargo complex at branch points. We are investigating microtubule geometry at the PLM branch point by observing EBP-2 dynamics across developmental stages, as the neuron branches and grows.

Across vertebrate and invertebrate systems, it is observed that neurons exhibit complex cellular morphologies by extending processes that form branches. However, little is known about whether pre-SVs tend to distribute randomly across all branches or exhibit a preference toward certain branches over others. We address this question using the Posterior Lateral Microtubule (PLM) cells of the model organism C. elegans. Using live imaging, we examined transport of pre-SVs in the PLM process at the branch point using multiple markers specific for pre-SVs. We observed that ∼50% of anterogradely moving pre-SVs enter the collateral branch, while only ∼15% go straight along the main process. We find that immediately upon laser ablation

of the synapse, pre-SVs show reduced preferential turning into the synaptic branch (∼15%). Since the physical presence of the synapse is necessary for turning, we investigated the role of genes important for synapse specification in regulating turning behaviour of pre-SVs. We find that in the absence of proteins required for active zone assembly, viz. SYD-1/Rho-GAP, SYD-2/Liprin-α, UNC-10/RIM-1 and ELKS-1, pre-SVs show reduced turning into the synaptic branch (∼15%). These findings suggest that the synapse regulates transport of pre-SVs at branch points from a distance. We propose that the synapse sends a retrograde signal, likely activated downstream of SYD-2/ELKS-1 assembly, which may interact with the cargo-motor complex and direct it into the synaptic branch. Consistent with this hypothesis, we find that preferential turning is lost in reduced levels of DHC-1 (subunit of Dynein motor complex). We further find that in the absence of DLK-1, a MAPKKK important for neuronal regeneration, turning is reduced to ∼20%. We propose that DLK-1 is potentially the retrograde signal that causes preferential turning of pre-SVs into synaptic branch.

2.3 Anindya Bhattacharjee

Smelling Time - Does it Matter?

Decisions are made during and/or after sampling specific sensory stimuli in noisy surroundings. Taking some time to gather more information may lead to better decisions. Information accumulation is well documented in vision and somatosensory systems. However, in the olfactory system there is no clear contention on the prevalence of information accumulation. While many studies report longer discrimination times for highly similar odors, few of them argue that rodents take decisions within single sniffs and subsequent sniffs don't improve the accuracy. In this study, we asked whether olfactory performance varies if the stimulus is provided for different durations. By reducing the stimulus duration and response time window, we see that speed pressure affects the learning in the simple tasks. However, when provided with sufficient response window, the learning deficit is rescued. Further we show that when the stimulus duration is reduced for difficult discrimination tasks, the olfactory learning and memory are impaired. The reduced performance is seen when the animals spend less time sampling the odor stimulus. Thus, we provide a concrete evidence as to how longer sampling affects olfactory guided behaviors. Our results also showcase the existence of information accumulation in the olfactory system.

2.4 Anshul Assaiya

Structural and Functional studies on Drosophila Ionotropic receptors

Ionotropic receptors (IRs) in Drosophila is a recently discovered family of membrane receptors which is responsible mainly for chemosensation. These receptors share considerably high degree of sequence similarity with ionotropic glutamate receptors (iGluRs) leading to a similar modular organization. Different members of this family show diverse functions such as temperature sensation, hygrosensation and circadian rhythm resetting. Thus, IRs resemble GPCRs in terms of function and iGluRs in terms of modular organization. This family has been divided into two classes- IR coreceptors, which have complete amino terminal domains (ATDs) and Odor specific IRs in which ATDs are truncated. Previous reports show that IR coreceptors are necessary for stability and localization of functional receptors on the membrane. The molecular basis of the expression, assembly, and colocalization of functional ligand gated ion channel by IRs is still not defined and structural studies will reveal the mechanism of their assembly and the functional parallels with the iGluRs. To investigate the underlying mechanisms, various members of this family and their domains have been cloned and their expression and purification optimization is ongoing for carrying out crystallization trials and cryo EM studies. Functional analysis of IRs will act as a promising model system to understand the evolution of diverse odor recognition and signalling properties. Moreover, the modular organization of IRs provides an opportunity to selectively modulate their odor specificity, ligand recognition and localization, this will also provide important insights into how olfactory receptors achieve a diverse ligand specificity.

2.5 Arun Neru

Theta oscillations are required to generate spatially periodic receptive fields in the medial entorhinal cortex

Grid cells in the medial entorhinal cortex (mEC) fire at the vertices of a hexagonal grid that tiles the entire space an animal explores. This pattern serves as an allocentric coordinate system for animals to integrate their movement and determine their current location even in the absence of external cues. The stability and precision of this pattern is remarkable given many experimentally measured variables in the mEC - inputs to stellate cells and variability of local field potential oscillations - vary noisily as the animal navigates its environment. How can a stable spatial representation be built upon such shaky ground? We discover that the answer lies in the interplay between theta oscillations and the intrinsic time scales of the system, namely, the conductances expressed in stellate cells. To illustrate the mechanism we simulate a network of physiologically detailed conductance based model stellate cells coupled via inhibitory interneurons. Competitive interactions between stellate cells cause different groups of neurons to fire at different times. The identity of neurons that form transiently synchronous groups is determined by the topology of inhibition and the history of activation of stellate cells. We show that these spatiotemporal sequences can be easily perturbed by noise to the network. Theta oscillations are required to ensure that the same sequence is stimulated every time the animal traverses a particular trajectory. The reliability of these temporal sequences, in turn, translates into the stability of the grid cell's spatially periodic receptive field. Theta oscillations are themselves fickle, in that, the phase of theta is not pinned to the location of the animal as the spiking activity of grid cells are. Further, changes in movement velocity affect the frequency of theta oscillations. We show that these perturbations to theta do not affect the stability of grid fields. Our simulations concur with experimental data demonstrating that when theta oscillations are selectively and reversibly removed by excising input from the medial septum, grid fields dissipate leaving spatially non-specific and temporally imprecise patterns of activity. Our model shows that the formation of spatially periodic receptive fields is an emergent property of the coupling between theta oscillations and the intrinsic rich temporal repertoire of the mEC network.

2.6 Bharath Krishnan

A mechanism of novelty detection by medial entorhinal cortex circuits

Bharath Krishnan, Arun Neru and Collins Assisi

Grid cells are neurons present in the Medial Entorhinal Cortex (MEC) that fire action potentials whenever the animal is positioned at the vertices of a tesselating hexagonal grid. There exists strong evidence to suggest that grid cells constitute the neural substrate for performing path integration in navigating animals. Experiments performed in different environments demonstrate that novel surroundings tend to disrupt the symmetry and regularity of these hexagonal grid patterns. This disruption in hexagonal symmetry has been shown to be concomitant with a shearing of individual grid cell receptive fields. Upon gaining familiarity with the environment, the grid patterns revert back to their original scale and symmetry.

Electrophysiological recordings from stellate cells present in layer II of the MEC (putative grid cells) have demonstrated that these stellate cells are connected via inhibitory interneurons that show Spike-timing-dependent plasticity (STDP). The existence of STDP at these Inhibitory-Excitatory synapses might play a role in progressivley evolving the functionality of the network.

In this study, we delineate the mechanisms underlying the formation of these grid-cell patterns by studying the properties of an MEC network. The individual neurons in our network are modeled as biophysically realistic conductance-based Layer II Stellate cells. The topology of our network is similar to the network topologies described in existing Continuous Attractor models of Grid cells. Under particular constraints, we show that Stellate cells coupled via inhibitory intermediaries can mutually inhibit each other. We further demonstrate that STDP, which plays the role of continually reshaping the topology of the network; coupled with modulations in the theta rhythm from the medial septum can encode for and represent the novelty and familiarity attributes of an environment.

2.7 Deepanjali Dwivedi

Spike timing precision and reliability in a mouse model of Fragile X syndrome

Studies done for cortical networks, hippocampal slices and cultures have put forward the idea of 'reliability' and 'precision' in spikes produced by a neuron, for repeated trials of same current stimuli. Studies have shown that reliability and precision of producing spikes by a neuron is higher in a noisy stimulus and these parameters drop in the presence of an excitable network and in altered functioning of some channels. Fragile X disease is associated with increased network excitability and malfunctioning of different ion channels. The hypothesis is 'the reliability and precision of spikes in hippocampus CA1 are impaired in Fragile X syndrome mice models'. Our experiments show that precision in spike response from a neuron is a developmental profile such that adult diseased animal model have more imprecision than younger ones, but only when the input stimuli is a step input. In fluctuating input current stimulus the spikes are very precise for both WT and diseased mice. There is an overall reduction in excitability for KO CA1 cells and mAHP, sAHP were found to be significantly elevated in diseased CA1 cells.

2.8 Dipanjan Ray

Neuroplastic changes in the visual dual stream system during perception and action

Dual stream hypothesis is a pre-eminent theoretical approach to conceptualize visuo-motor information processing. Subtle variations of the model exist often leading to fundamentally divergent explanations of underlying neural mechanisms. For example, the Mishkin-Ungerlieder (MU) model suggest that the input information decides the neural pathway for processing. Position related information ('where') takes the dorsal stream comprising MT/V5 and parietal cortex whereas finer feature processing ('what') comprising color, face, etc takes the ventral stream involving V4 and inferior temporal areas. Concomitantly, the Milner-Goodale (MG) model suggests that the task goal decides the processing pathway, with dorsal stream areas needed for visual (sensory) guidance of action that doesn't involve active perceptual processing whereas the ventral stream is recruited for perceptual object processing. No single study has evaluated the viability of each model in a overarching experimental design. Furthermore are the models subject to neuroplastic changes is an open question. We addressed these issues in an fMRI experiment involving 20 right-handed human volunteers (20-34 years, 12 females). Participants were scanned with TR=2 s TE= 35ms, flip angle =90° while each of them was performing 3 visual perception tasks and 3 visuo-motor action tasks inside a 3T MRI scanner. For both categories, 2 tasks were designed to involve "what" (color, face) processing and 1 task required processing of "where" (position) information. The fMRI scans were repeated after seven days of the practice session outside the scanner to explore the neuroplastic changes. In all perception tasks, bilateral ventral stream areas are activated, whereas all action tasks shows prominent activations in bilateral primary visual cortices, ventral and dorsal stream regions. Unlike color and face perception, position perception elicits additional activations in dorsal stream areas. Deactivation of BOLD signals were observed in medial dorsal stream areas and in few primary visual and ventral stream regions in all perception tasks. Analysis of reaction times established the positive effect of practice. Number of voxels activated decreased with practice but no such decrease was observed for deactivated voxels. Dorsal stream activations in orientation perception could not be explained by the MG model whereas ventral stream activation in same condition violated the MU model predictions suggesting the need for a coupled perception-action model of visual processing. Deactivation found in perception tasks further points towards the role of feedforward and feedback interactions between both streams.

2.9 Divyansh Mittal

Degeneracy in the robust expression of spectral selectivity, subthreshold oscillations and intrinsic excitability of entorhinal stellate cells

Neurons in layer II (LII) of rodent medial entorhinal cortex (MEC) have been implicated in spatial navigation, especially with cells there known to act as grid cells that elicit action potentials in a grid-like pattern as the animal traverses an arena. Several theoretical and computational models have been proposed for the emergence of these grid cells, and have been tested from different perspectives with varying degrees of success. A common lacuna in these models relates to the systematic assessment of the impact of biological heterogeneities on the robust emergence of grid cells. An essential step in filling this lacuna is to build a conductance-based model population that efficaciously incorporates electrophysiologically-observed heterogeneities in channel expression and intrinsic properties of MEC neurons. Here, we employed a multi-parametric multi-objective stochastic search algorithm, which involved creating model neurons by randomly picking values for 55 active and passive parameters of LII MEC stellate cells. We subjected this stochastically-generated model population to validation based on the 10 electrophysiological measurements from stellate cells, and found 155 of the 50,000 stochastic models to fulfill all validation criteria. This valid model population exhibited significant heterogeneity in the 55 underlying parameters with weak pairwise correlations, despite manifesting robust theta-range intrinsic sub-threshold membrane potential oscillations (MPOs), and matching resonance and intrinsic properties of stellate cells. Next, employing virtual channel knockouts on this valid model population, we demonstrate electrophysiological equivalences in this valid model population, whereby the expression of MPOs and resonance was differentially reliant on HCN and M-type potassium channels. However, knockout of the persistent sodium channels eliminated MPOs, and there was a differential and variable dependence of all measurements on different channels. Finally, employing this valid model population, we computed the spike triggered average and quantitatively predict theta-range (3–12 Hz) spectral selectivity and gamma-range (25–150 Hz) coincidence detection capabilities for inputs afferent onto MEC stellate cells. Our results establish significant degeneracy in the robust expression of spectral selectivity, subthreshold oscillations and intrinsic excitability of MEC stellate cells, and proffer a physiologically-constrained heterogeneous model population as an efficacious substrate for the incorporation of intrinsic heterogeneities into network models.

2.10 Gaurang Mahajan

Internal calcium stores and calcium regulation in CA1 spines

A transient rise in calcium (Ca2+) at the post-synaptic locus is necessary for inducing long-lasting changes in synaptic efficacy. Models for activity-dependent plasticity (LTP/STDP) have traditionally attempted to link the direction and magnitude of synaptic changes to the properties of the Ca2+ time course (Ca2+ control hypothesis). In these models, NMDA-R and voltage gated (VGCC) channels on the plasma membrane provide the only sources of Ca2+ into the cell. However, intracellular stores in the endoplasmic reticulum (ER), which is present in dendritic processes, can also potentially contribute to shaping the Ca2+ signal in the post-synaptic spine. Several lines of experimental support in fact exist for an involvement of ER stores in Ca2+ handling at active spines and downstream effects on plasticity. EM studies have shown ER being present in individual spines as well as dendrites, and its extent could vary dynamically in response to Ca2+ fluctuations. Despite considerable experimental work, there is still lack of clarity on the factors governing extent and distribution of ER in spines, and what novel/additional properties ER stores may confer on synapses. We have computationally explored the contribution of Ca2+ release from the ER to calcium signaling at the post-synaptic locus. Using a biologically realistic model of a CA1 spine, we consider ER Ca2+ release from IP3 receptor-gated channels (IICR) under different stimulation conditions. Our preliminary findings suggest selective enhancement of the depression window by IICR, whose modulatory effect is diminished at LTP-inducing stronger stimulation. These results point to a possible contribution of internal Ca2+ stores, which is over-represented in larger mushroom spines, in stabilizing potentiated synapses.

2.11 Harjot Kaur

Study of Dendrite Regeneration using C. elegans Model

Both dendrites and axons are vulnerable to physical insults during the life span of an individual. Several studies recently have focused on understanding the regenerative capacity of an injured axon. The p38 MAP kinase signaling cascade involving Dual Leucine zipper kinase DLK-1 is essential for axon regeneration. The cyclic AMP and mTOR signaling are limiting factors in axon regeneration. But less is known about dendrite regeneration. In Drosophila melanogaster, studies reveal that PTEN-Akt pathway plays an important role in dendrite regeneration while its independent to DLK-1 signaling. To understand the mechanisms of dendrite regeneration, I used PVD neuron in C.elegans, which has branched dendrites. The PVD neurons are responsible for harsh touch sensation. Using femtosecond laser, I severed the dendrites and axon initial segment (AIS) of this neuron. After the primary dendrite was severed near the cell body, I noticed sprouting of new branches from the cut site at 3-hour. By 24-hours the primary dendrite regrew, following similar trajectory and formed more complex branching patterns unlike the original menorah observed in uninjured PVD. These branches often lacked self-avoidance phenomenon. I quantified the regeneration pattern in two aspects - length of primary dendrite and number of branches. The primary dendrite regrew in length by 83.5$\pm$64.7 μm and 201.1$\pm$56.1 μm at 24-hour and 48-hour respectively. This was half the length of uncut dendrite. Severing the AIS led to complete retraction of the proximal axon after 3 hours. This was followed by the formation of a new process either from cell body or from sites of primary dendrites adjacent to the cell body. Eventually, these processes were guided to the ventral nerve cord. This response is reminiscent to the repolarization phenomenon observed in fly and vertebrates after cutting AIS. The extent of regrowth of the primary dendrite and the number of branches were not affected by the loss of dlk-1. This indicated that dendrite regeneration is independent of dlk-1 as seen in fly. My future goal is to identify signaling mechanism that is important for the dendrite regrowth. Further, I want to correlate dendrite-remodeling responses with behavioral aspects of PVD neuron.

2.12 Jyoti Kumari

Structural Insight into Regulation of Kainate Receptor Functions via their Auxiliary Proteins

The tetrameric ionotropic Glutamate receptors (iGluRs) mediate majority of excitatory neurotransmission in central nervous system. They have been grouped into three classes namely AMPA, NMDA, and Kainate receptor depending upon their agonist binding affinity. Dysfunction of these receptors are associated with many neurological diseases. Functions of these receptors are tightly controlled via different regulatory mechanisms. One of the important regulatory pathway is by interaction with their cognate auxiliary proteins at post-synaptic membrane. Hence it is important to understand the mechanisms of regulation of the receptor in details. Our lab is interested in understanding how iGluR functions are modulated by their auxiliary proteins. One of the project in our is to understand regulation of Kainate receptor via Neto (Neuropilin and Tolloid like proteins) protein which regulate gating functions as well as trafficking and distribution of Kainate receptors to the synapses. Lot of work has been focused towards electrophysiological recordings to dissect mechanism of regulation. However, structural insights into regulation, stoichiometry, and primary interaction sites for these complexes is lacking. Towards this goal, we have optimized recombinant expression and purification of Neto1 proteins from mammalian cells. Simultaneously, Kainate receptor, have been purified to homogeneity from baculovirus mediated expression in insect cells. We have been successfully able to reconstitute the complex in vitro and have carried out structural analysis via negative stain and Cryo Electron Microscopy of the complex. Our structure gives first insights into mechanistic regulation of kainate receptor via Neto1 protein. We are also verifying the structural findings with help of electrophysiology.

2.13 Kambadur Ananthamurthy

Mapping Time to Hippocampal CA1 Sequences

Small populations of Hippocampal pyramidal neurons from the CA1 are known to take part in reliable, time-locked, activity sequences. In trace memory experiments, we have earlier shown that the interval between the conditioning stimulus (blue LED flash) and the unconditioned stimulus (a puff of air to the eye) is represented by a sequence of activity of these neurons. A subset of these neurons is triggered by the initial stimulus, and then successive subsets become briefly active in succession to bridge the time gap between the two stimuli. We are interested in further understanding these CA1 activity sequences, by asking,

1. How stable are the sequences over time?
2. How does changing the Inter-Stimulus Interval (ISI) affect the population of CA1 neurons that participate in the response?
3. How do responses evolve with habituation and re-learning?

In our experimental design, we train head-fixed mice to a Trace Eye-Blink Conditioning task as described above, where a blue LED flash (CS) is followed after an interval by an air-puff to the eye. We use programmed microcontrollers (Arduinos) to deliver stimuli and synchronize video recording of eye-blinks. The animals that learn the task exhibit conditioned responses such that their eye-blink begins just before the expected air-puff.

To study the activity in the CA1 network, we utilize optical imaging of activity from transgenic mice expressing the calcium reporter GCaMP6f. We image the Ca2+ activity using a custom-built two-photon microscope with galvanometric scanning at a frame rate of 10-15 Hz. We monitor the activity of $\sim$100 cells in each field of view, in vivo. In order to monitor the evolution of responses, we perform multi-day recording of activity from the same cells, coupled with the behaviour.

2.14 Kriti Chaplot

SOD1 modulates VAPB aggregation via ROS in a Drosophila model of ALS

Amyotrophic Lateral Sclerosis (ALS) is an incurable, late onset motor neuron disease, strongly linked to various causative genetic loci (Andersen and Al-Chalabi, 2011). One such locus, ALS8, codes for a missense mutation, P56S, in VAMP-associated Protein B (VAPB) (Nishimura et al., 2004) that causes the protein product to misfold and form cellular aggregates (Teuling et al, 2007; Ratnaparkhi et al, 2008). Aggregation is a common feature among most neurodegenerative diseases and might be a contributor or a consequence of disease pathogenesis (Blokhuis et al, 2013). Here, we identified 57 genetic modifiers of ALS8 aggregation in an RNAi screen targeting 900 unique genes belonging to different categories or families associated with ALS or VAPB function, performed in a Drosophila S2R+ cell line expressing the homologous VAP(P58S) mutant protein. The modifiers included other ALS loci, ALS related genes and elements of TOR signaling pathway. We validated one such modifier, superoxide dismutase 1 (SOD1), in Drosophila melanogaster models of ALS8 (Ratnaparkhi et al, 2008; Devasigamini et al, 2014; Moustaqim-Barrette et al, 2013) by measuring changes in VAP(P58S) aggregation in the third instar larval brain. SOD1 is the oldest known ALS locus, ALS1 (Rosen et al., 1993), functionally responsible for reducing cellular reactive oxygen species (ROS). In this study, we describe an ROS-dependent modulation of VAP(P58S) aggregation kinetics mediated through SOD1. Further mechanistic insight in understanding the interaction between ALS1 and ALS8 will help identify therapeutic targets.

2.15 Kumari shweta

FGFR/Heartless negatively regulates Fog signalling in Drosophila nervous system

GPCRs are the most diverse group of transmembrane receptors involved in a mediating a wide range of signals from light to small molecules inculding neuropeptides, small molecules like odorants and steroids. Folded gastrulation (Fog) is a secreted ligand which signals via a GPCR to regulate cell shape in the ventral epithelial cells of the blastoderm embryo, to facilitate gastrulation. In the embryonic CNS, loss of fog leads to motor axon guidance defects; knock-down of fog in glia leads to defects in ensheathment. While to mechanism of Fog signaling during gastrulation has been studied in some detail, its regulation is still poorly understood. We are interested in the role of Fog signaling and its regulation in the context of the embryonic CNS. In this study, we have examined the interaction between Fog and FGFR/Heartless (RTK) signaling pathways. Both, Fog and FGFR/Heartless appear to have similar effects on glial morphology that prompted us to determine if these two pathways interact. Using genetic epistasis we find that FGFR/Heartless signaling indeed regulates the Fog pathway. In my poster, I will describe this work and also discuss the possible mechanism by which these two pathways might be interacting.

2.16 Manal Shakeel

Using sugar-elicited search behaviour to study path integration and visual landmark learning in Drosophila melanogaster

Insects are highly capable and efficient navigators. Food search paradigms can be used to study navigation and its components. We have established a set up to study sugar-elicited search behaviour, a particular form of local search (Dethier 1957, Brockmann et al. in revision, Murata et al., 2017). Typical search behaviour is initiated after consumption of a small amount of sugar solution by a hungry fly. The behaviour is characterized by high turning rate during walking and making returns to the location of sugar drop. Our experiments show that flies make precise returns to the location of the sugar drop, even in the absence of visual and chemosensory information. This indicates that flies can use self-motion cues and path integration to find their way back to the sugar drop. Next, we want to block proprioceptive sensory neurons to test whether flies use stride information for path integration. Furthermore we want to explore the role of visual landmarks in guiding navigation during the local search. First, we tested whether the presence of visual cues in the arena modulates the search behaviour. We found that flies show heightened visual attention and signs of learning. Then we started experiments testing whether flies are capable of learning the geometry of landmarks similar to what has been shown for honey bees (Cartwright and Collett, 1983) and ants (Collett et al., 2003). It is assumed that insects store 'snapshots' of the visual landmarks and use that for navigation and goal localization. We placed the sugar drop at a specific position defined by an array of two cylindrical landmarks. The arena had a second set of identical landmarks without any food to test if the flies have learnt the position of the sugar drop with respect to the two landmark. Pilot experiments indicate that flies may be learning and orienting to the geometry of the landmarks. We propose that the small scale sugar elicited search could be used as an experimental assay to study the neural and molecular mechanisms underlying path integration and landmark memory.

2.17 Maurya Nehakumari P

Identification and analysis of glial enhancers in folded gastrulation

Mechanisms that generate neuronal diversity have been studied extensively in Drosophila and some of these are conserved. In comparison, less is understood about how glial diversity is generated. In vertebrates, glia can be classified into four major categories: Astrocytes, Oligodendrocytes, Schwann cells and microglia. Functional representatives of each of these classes exist in Drosophila. To understand mechanisms involved in generating glial diversity we have taken an approach that involves identifying enhancers that drive expression in different subsets of glia, and subsequently the factors involved in mediating expression.
Fog or folded gastrulation is secreted signaling molecule that drives invagination during gastrulation and regulates cell shape change. In the embryonic CNS, fog is expressed, amongst others, in a subset of longitudinal glia. Through generation of enhancer::reporter lines, we have identified an enhancer in fog that drives expression in ventrally located cell body glia in abdominal segments. We are analyzing the expression of this reporter line through embryonic development and conducting a sequence analysis to identify potential regulators. Some of these studies will be discussed in the poster.

2.18 Meenakshi Pardasani

Effect of early life stress on olfactory guided behaviour in mice

Stressors of different kinds can modulate various mechanisms in different brain regions. Adult Neurogenesis which occurs in Hippocampus and Sub-Ventricular Zone (SVZ-OB) is one such process which is known to be affected by stress. In case of SVZ-OB Neurogenesis, recent study indicates decreased turn-over of neurons and subsequent olfactory deficits in corticosterone administered mice. However, the association between stress and observed behavioural impairments are not yet deciphered. In our laboratory, we use maternal separation as an early life stress model in mice. Tactile stimulation in the form of licking, temperature regulation, suppression of Hypothalamo-Pituitary-Adrenal (HPA) axis, olfactory cues in addition to nutritional enrichment from mother to pups are certain important aspects of maternal behaviour. Early life stress via maternal deprivation is known to result in rather persistent changes in anxiety-related behaviours. We are currently assessing the olfactory detection and discrimination abilities of animals using olfactory psychophysical experiments. This includes freely moving and head restrained go/no go associative odour discrimination tasks and conventional paradigms such as cage digging-in tests. Stress induced effect on SVZ-OB adult neurogenesis is also being checked. Finally, we plan to use the optogenetic strategies to modulate the functions of responsible circuits to get the causal relationships with the observed behaviour.

2.19 Meenakshi VKC

To understand and elucidate the neuronal basis of bi-lateral transfer of olfactory memory between two lobes in Apis dorsata brain

Left right symmetry is present in large parts of brain across phyla and often there are specific set of neurons that connect the two sides. Inputs through sensory organs on one side of the organism are confined to one side of the brain for quite a number of synapses. However the information is available on the contralateral side for various purposes as evident from behavioural studies. The mechanism underlying this bilateral transfer is not understood. In A. mellifera, upon classical conditioning using PER paradigm, the honey bee exhibited long term memory for upto 72 hours (Scholl et al., 2015). In Apis mellifera, on training with conditioned stimuli (CS) on one side, though the memory is initially only on the trained side, it is present bilaterally after 3hrs. Our lab has previously shown that there are no anatomical connections from the antennal lobe on one side to the contralateral Mushroom body calyx, which is the important center for olfactory conditioning in insect brain (Unpublished data). We are using Apis dorsata which is native to South-East Asia to elucidate the mechanisms involved. We have standardized the bilateral transfer behaviour paradigm. We also aim to localize molecules in the MAPK pathway and a well-known molecular memory switch CaMKII across the bee brain in order to further investigate if these molecules play a role in this transfer of information.

2.20 Neena Ratnakaran

UNC-16/JIP3, along with downstream protein LRK-1/LRRK2, is necessary for the polarized distribution of synaptic vesicle proteins

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Neurons are highly polarized cells with discrete dendritic and axonal processes. Sorting and transport of distinct molecules into either of these compartments may play an essential role in setting up of neuronal polarity. We show here that UNC-16/JIP3, present at the Golgi, plays a critical role in sorting of diverse proteins including synaptic vesicle proteins (SVPs). In unc-16 mutants, SVPs are mis-trafficked into dendritic processes and are transported in aberrantly formed compartments of irregular size and having uncharacteristic protein composition. Our studies indicate that UNC-16-dependent localization of SVPs depends on LRK-1, a homolog of LRRK2/PARK8. In unc-16 animals, LRK-1 localization on the Golgi appears to be reduced while over-expression of LRK-1 in unc-16 is able to rescue specifically the SVP trafficking defects. These observations suggest that LRK-1 is a downstream effector of UNC-16 in the trafficking of SVP transport carriers. Further, our study indicates that UNC-16 and LRK-1 mediated Golgi-localization of the μ-subunit of AP-1 complex plays a role in regulating the size of SVP transport carriers, while another adaptor protein, the AP-3 complex, regulates the composition of the SVP transport carriers. Our study, thus, describes a novel role of UNC-16 in polarized sorting of multiple proteins. Additionally, we identify a series of steps through which UNC-16, LRK-1 and downstream adaptor proteins regulate the trafficking of SVPs. We hypothesize that mis-sorting of SVPs in the absence of the UNC-16 and LRK-1 regulator proteins could lead to changes in neuronal polarity.

2.21 Nisha Ann Viswan

AutSim: Modeling activity-driven synaptic cell biology in health and disease

Autism is a set of complex developmental disorders caused by genetic mutations and errors in biochemical signaling networks, that leads to discrepancies in synaptic function. Our work aims to integrate various studies to develop a framework of models closely linked to a database of experimental measurements for systematic refinement and validation. The AutSim framework is designed to help understand synaptic events in neurons from control and autism-spectrum disorder animal models, such as Fragile X syndrome and SynGAP1 knockout rodents. We have established a pipeline for running the models on a database of experiments. Each simulated experiment generates a score for accuracy, which is used to refine the models. The current model has over 500 molecules and reactions, and focuses on synaptically activated biochemical cascades (such as EGFR, mGluR, BDNF, ß2AR and AMPAR internalization pathways) leading to protein translation and thereby establishing plasticity [Jain P and Bhalla U.S., 2009; Bhalla U.S. and Iyengar R, 1999]. Our long-term goal is to use the model for making pharmacological predictions such as acute and chronic drug treatments, and also address genetic compensatory effects in control and diseased states. We plan to open-source the model library, database, and pipeline to the scientific community for use, refinement and extension.

2.22 Niyoti Tembulkar

Olfactory deficits in a Parkinson's disease mouse model

Parkinson's disease (PD) is a neurodegenerative disease resulting from death of dopaminergic neurons in substantia nigra. Alpha synuclein, particularly in its abnormally folded forms, is implicated in the pathogenesis of PD. Braak and colleagues have observed that in most cases of PD the alpha synuclein aggregate pathology spreads in a specific pattern starting from olfactory system and gut. It has been reported that olfactory dysfunction is one of the early symptoms observed in patients with neurodegenerative diseases including PD. Moreover, the presence of misfolded protein inclusions was found at the level of olfactory sensory neurons in PD patients. To study the neurological disorders in detail, it is essential to investigate the disease pathophysiology at molecular level and correlate it with the behavioural deficits observed at different stages of disease progression. Here we are trying to develop a Parkinson's disease mouse model by the local injection of Alpha synuclein aggregates (both in oligomeric and fibrillar forms) in different centres of olfactory pathway. Our preliminary results show the smelling deficits in the animals injected with alpha synuclein fibrils in the olfactory bulb (OB) compared with control mice. Therefore, to unravel the mechanisms underlying the olfactory deficits observed in our model, we are planning to investigate the pathophysiological changes caused by aggregated alpha synuclein at the cellular level.

2.23 Pavithraa Seenivasan

Efficient Phase Coding And Excitability Robustness Within The Degeneracy Framework

Hippocampal place cells encode space using both rate and temporal codes. Whereas a rate code is defined by a marked increase in the firing rate of a neuron within the place field, the associated precession of neuronal firing relative to the hippocampal theta rhythm characterizes a phase code. This implies that the phase code, and not the rate code, is endowed with a monotonic dependence of the coded representation on spatial location within the place field. We postulated that this monotonicity confers upon the phase code an enhanced potential for information transfer, and explored phase coding from the perspective of the efficient coding hypothesis that relates neuronal representations to information maximization. We approached this question within the framework of degeneracy, a principle that states that disparate structural components could yield similar functional properties. In doing this, we first built a conductance-based phase coding model, defined and quantified the efficiency of a phase code within an information theoretic framework, and employed this framework to assess the neuronal characteristics that would maximize encoding efficiency. We recruited a multi-parametric stochastic search strategy to generate numerous models that span a wide range of intrinsic parameters to mimic the inherent channel heterogeneities and to alleviate problems associated with parametric bias. We assessed the efficiency of spatial information (from within a single place field) transfer through phase precession in these distinct models. We found that comparable levels of high-efficiency information transfer could be achieved across these models with strikingly disparate intrinsic properties, thereby establishing the expression of degeneracy in efficient phase coding. Finally, we asked if these models that were capable of efficient information transfer were also robust in terms of their intrinsic excitability properties. Specifically, we imposed an additional layer of constraints on these efficient models with reference to electrophysiological measurements of CA1 pyramidal neuronal excitability. We found that resultant models displayed both phase coding efficiency and robust intrinsic excitability signatures, with distinct parametric combinations yielding similar functionality. Together, our results unveil significant degeneracy in the ability of a neuron to concurrently achieve a highly efficient encoding system and maintain robustness in intrinsic electrophysiological signatures.

2.24 Pragya Pandey

Differential saccade planning in search and triple-step paradigm

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Serial order of movements may be resolved endogenously or exogenously. In the former case, the sequence of movements is implicitly determined by the agent, for example, during dialling a phone number or playing piano. In case of exogenous serial ordering of movements, the sequence is determined by the environmental stimuli, for example, rapid shooting at consecutive pop up targets. Fast eye movements, called saccades, may also be generated in series to find out and foveate the object of interest. Although gaze shifts sequentially, a pair of saccades may be planned simultaneously (Becker and Jürgens, 1979; Ray et al., 2004). In contrast, other studies suggest that a series of saccades in a sequence are planned and organized before the first saccade in the sequence is executed (e.g., Zingale and Kowler, 1987). In this study, we investigated how the ordering of saccades in sequence, that is resolved either exogenously or endogenously, influences saccade planning. In the first task (exogenous), after a stipulated period of fixation at the centre of the display monitor, a set of one to three identical green square(s) appeared sequentially at the periphery. Participants were instructed to follow the order of the appearance of the target(s) by orienting their gaze. In the second task (endogenous), participants searched for a target human face in a set of human faces with neutral emotional expression. Participants oriented their gaze to the target face by making maximum three saccades in an order they wished. The data suggest that exogenously ordered only first two consecutive saccades were planned in parallel. The extent of parallel processing was observed in last $\sim$150 ms of saccadic reaction time. On the other hand, all pairs of consecutive saccades were planned one after another when ordered endogenously during search. This result indicates that the way our brain resolves ordering of movement directions can influence the dynamics of planning movements, and our oculomotor system indeed is limited in capacity to get more than two saccades ready simultaneously.

2.25 Pratyush Ramakrishna

Phase relationships of High-Threshold bursting Thalamocortical neurons and their role in modulating Alpha oscillations

A subclass of Thalamocortical neurons called High-Threshold bursting Thalamocortical (HTC) neurons have been implicated as the potential source of Alpha oscillations in the Thalamus. These neurons have inherent channel properties that ensure that each cell fires at approximately 10 Hz even when the cell is disconnected from the rest of the network. It has also been found that acetylcholine and network inputs can modulate this intrinsic rhythm. These HTCs are coupled via gap junctions allowing them to synchronize. Extant data suggests a connectivity profile of these cells wherein at most 4 cells are seen to be directly coupled to a single cell. Robust alpha oscillations as seen in the thalamus keenly constrains the strength of these connections. Based on these observations, we propose a network motif of HTC cells that includes a biophysically realistic description of ion channels that orchestrate the individual rhythms. This allows for a large population of HTC neurons to be entrained to produce the characteristic 10 Hz oscillation. Separately it has been observed in experiments that injecting external current introduces phase differences while maintaining phase locking. Our model, with the predicted network motif accurately reproduces these phase relationships in response to current injection. Furthermore, we propose that ambient acetylcholine levels could modulate the phases of individual cells leading to a modified spectral behavior of this network. A transition from a single peak at 10 Hz to dual peaks at 10 Hz and 20 Hz within a few hundred milliseconds is seen in EEG recordings in behavioral tasks requiring attention. The rate at which the switching of frequency bands take place suggests that intrinsic channel properties of HTCs alone cannot orchestrate the change. Our model provides a biophysical basis for this surprisingly rapid transition without disrupting the intrinsic rhythm of individual cells.

2.26 Sandeep Kumar

Overcoming the age-related decline in neuronal regeneration with exercise

Our nervous system has limited capacity for regeneration after accidental damage. The capacity of axon regeneration declines with age (1). Many efforts have been made in identifyng the molecular pathways responsible for inhibiting neuronal regenration. However, limited progress using drug is made to provide cure for the devastating consequence of nervous system injury. On the other hand, rehabilitaion has shown great promise in improving the health conditions of the patients those have undergone spinal cord or other neuronal injury (2). However, it is not understood how rehabilitation helps functional recovery.

Caenorhabditis elegans is a good model to study neuronal regeneration, as axonal processess in worm can be severed with laser. Recently, our group has shown that functional restoration after injury of touch neurons decline with age in worm (Basu et al., 2017- under revision). Here, I asked whether exercise such as swimming could help in the functional recovery in aged conditions. I have used neurons for gentle touch sensation as a model for the experiments related to behavioral recovery. As seen before, I have also found that the functional recovery in posterior touch sensation following axotomy of PLM neuron is significantly reduced after 3 days of ageing. In order to mimic exercise, I subjected the worms in wells, where they swimmed for various duration ranging from 5 minutes to 3 hours. My data suggests that 90 minuites of exercise following axotomy helps overcome regeneration decline seen at 3 day old worm. I will investigate how exercise influences the cell-intrinsic and extrinsic mechanisms to promote functional recovery. This will be useful for further exploration of molecular, cellular and system level mechanism of rehabilitation therapies using C. elegans.

References

(1) Geoffroy, C. G., Hilton, B. J., Tetzlaff, W. and Zheng, B. Evidence for an age-dependent decline in axon regeneration in the adult mammalian central nervous system. Cell Rep, 15, 238-46 (2016).
(2) Thuret, S., Moon, L. D. F. and Gage, F. H. Therapeutic interventions after spinal cord injury. Nat. Rev. Neurosci. 7, 628–43 (2006).

2.27 Sarang Mahajan

Multisensory decision-making in rodents

In natural environment, animals gather information through their sensory systems and therefore the inputs from different systems can either integrate or compete with each other helping their perception and decisions. Multisensory decision making studies in rodents, employing audition and vision have supported the theory of inverse effectiveness. This theory suggests that if animals cannot make a decision based on the input through a single sensory system, animals use information through multiple sensory systems that may be complementary and helping the animals in making better and efficient decisions. Rodents rely primarily on olfactory and whisker systems for their survival and vital functions. Despite there are no reports unraveling if the information through these two sensory systems acts complementary to each other. Few studies have shown the synchronized activity while exploratory behaviour was performed through sniffing and whisking. This sets a strong basis to hypothesise that inputs from olfactory and whisker systems may integrate together leading to a specific behaviour. To test it we challenged the animals to discriminate between "olfacto-whisking" paired stimuli using a Go/No-Go paradigm. We observed that animals challenged with multisensory stimuli learned faster and showed better reaction times compared to the control animals. Thus, our results follow the theory of inverse effectiveness and support the idea of Multisensory enhancement.

2.28 Sasank Konakamchi

Stimulus dependent and sampling behavior (sniffing) independent odor discriminations in mice

Mice are known to be able to discriminate odors of varying complexities on fast but different time scales (∼250 - 380ms) depending on the similarity of odor stimuli they are challenged with. The similarity between different stimuli pairs can be judged by odor evoked spatio-temporal activity patterns of glomeruli residing in the olfactory bulb. Sniffing is a motor activity through which active sampling of odorants is controlled, on a time scale comparable to that of odor discrimination. In this study, we used different classes of olfactory stimuli – both simple monomolecular and complex mixtures of odorants to investigate the relationship between sniffing patterns and odor discrimination time. Mice were trained to discriminate between different odor pairs of varying complexity on a go/no-go task under head-restrained conditions and their breathing was analyzed during the stimulus presentation. While the animals took more time to discriminate between odors of higher complexity compared to simple odors, we found no correlation between the sniffing frequency and odor discrimination time.

2.29 Sashaina Fanibunda

Serotonin regulates mitochondrial function in cortical neurons

Neurons depend on mitochondria for critical neuronal functions- synaptic plasticity, neurotransmission, neuronal excitability and survival, yet the factors that influence mitochondrial physiology in neurons are poorly understood. Serotonin classically known as a neurotransmitter also modulates neuronal differentiation, growth and synaptic plasticity. However, the relationship between serotonin and mitochondrial physiology in neurons is currently poorly understood and explored. We hypothesized that serotonin may impinge on mitochondrial biogenesis and function. In cortical cultures, serotonin evokes a dose dependent increase in mitochondrial biogenesis and content, measured using mtDNA levels, mRNA and protein expression of specific mitochondrial markers and mitotracker staining. Further, serotonin also influences mitochondrial function, increasing ATP production, as scored by biochemical assays that measure cellular ATP content. An increase in basal and maximal respiration, as well as ATP production was observed in 5-HT treated neurons, using Seahorse-XFe analyzer. We have mechanistically identified the specific serotonin receptors, that mediate the effects of serotonin on mitochondrial biogenesis, using serotonergic receptor specific agonists and antagonists. While the 5HT2A receptor agonist DOI mimics the effects of serotonin, also increasing mtDNA and ATP production, pretreatment with a 5HT2A receptor selective antagonist MDL100,907 prevents the effects of serotonin on mitochondrial biogenesis and function. Downstream of the 5HT2A receptor, the major signalling pathways, that contribute to the effects of serotonin on mitochondrial biogenesis are the phospholipase C and MAP kinase pathways. In contrast, specific inhibitors of the PI3-kinase Akt signalling pathway, did not alter the effects of serotonin on mitochondrial biogenesis. Further, studies using a SIRT1 inhibitor EX-527, implicate SIRT1 in contributing to the effects of serotonin on mitochondrial biogenesis and function. The increase in mtDNA and ATP evoked by serotonin, may mechanistically be mediated by the recruitment of PGC1α, as evidenced by an increased transcription of PGC1α and increased PGC1α levels. Serotonin was also found to reduce cellular ROS levels, with a concomitant increase in the activities of SOD2 and catalase. Further, effects of serotonin were found to be neuroprotective against excitotoxic and oxidative stressors. These effects of serotonin on mitochondrial physiology may be relevant to the effects serotonin has on aging, growth, plasticity, and neuronal metabolism.

2.30 Sathyaa Subramaniyam

Cellular and network level selectivity of spatiotemporal input

In many forms of brain activity, ensembles of neurons fire sequentially, representing features of sensory stimuli, motor patterns, or internal computations. Hippocampal neurons exhibit sequential activity when animals are traversing a linear track, during replay events, trace conditioning and associative learning. In order to understand neuronal sequence computation for such diverse functional inputs, we study signaling processing at different levels viz, from subcellular levels to network level computations. Here we present modeling studies that focus on the various levels of neuronal computations: A) To examine how sequence computations may take place over multiple time-scales, we have modeled the role of different subcellular mechanisms and their interactions in discrimination of input sequences that vary in time and space. Selectivity of electrical and chemical signaling mechanisms for sequential inputs was previously shown. We are addressing interactions of such subcellular mechanisms along with electrochemical signaling (Calcium Induced Calcium Release; CICR) in sequence discrimination using abstract models. Attempts at modeling the cell wide response with detailed multiscale multicompartmental model including subcellular mechanisms and their role in discrimination of spatiotemporal inputs are ongoing. B) To study network computation of sequential spatiotemporal input, we have implemented abstract models of neurons with sequence-selective synaptic rules, to show discrimination of spatiotemporal inputs. We are investigating computational implications of the network populated with sequence recognizing neurons to parse various spatiotemporal inputs. These studies will demonstrate the neuronal computations at single neuronal and network level in discriminating various spatiotemporal input patterns.

2.31 Shekhar Kedia

Real-time Nanoscale Organization of Amyloid Precursor Protein in an Excitatory Post-synapse

The alteration in number and lateral organization of transmembrane molecules in post-synapse is considered as a crucial factor in health and diseases like Alzheimer's disease (AD). AD is the most prevalent form of dementia in the elderly. In the last decade a paradigm shift was observed towards understanding the molecular and biochemical pathways implicated in AD where the onset of the disease was proposed to be an altered function of synapses. This resulted in a careful evaluation of the biochemical pathways which regulate the Amyloid Precursor Protein (APP). Despite the enormous efforts, the finer mechanisms involved in the early onset of disease still remains unclear. This is partly due to the lack of in-depth evaluation of the mechanisms governing the spatial and temporal evolution of molecular machineries involved in the regulation, retention and recycling of APP. It is already known that genetic alteration of the APP is one of the major causes of Familial Alzheimer's Disease (FAD). Here we try to combine high density single particle tracking and super resolution imaging techniques like Photo Activation Localization Microscopy (sptPALM) and Direct Stochastic Optical Reconstruction Microscopy (dSTORM) to compare the organization and trafficking of wild type APP (APPwt) and a genetic variant of APP (APPswe) identified in FAD. We illustrate diffusional behaviour from thousands of spatially discrete single molecule trajectories from live neuronal cells with which it is possible to appreciate finer details of versatile molecular mechanisms pertinent in the organization and recycling of APP molecules at the membrane.

2.32 Shweta Tendulkar

Mon1 regulates dendrite arborization of da neurons in Drosophila

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The Drosophila da (dendritic arborization) neurons, is a class of peripheral nervous system associated sensory neurons that divided into four classes, Class I to Class IV, based on the increasing size of receptive fields as well as the arbor complexity, with the class IV da neurons being the most complex. The da neurons are excellent models to study patterning and remodeling as they show several unique properties like completely tiling the epidermal wall, which allows effective imaging.

A number of studies have elucidated sets of genes that modulate Dendritic Arborization. These include genes involved in endocytosis such as Rab GTpases, Tricornered (Trc), a conserved Ser-Thr kinase and Knot, a Collier family transcription factor. In this study, we find that Drosophila Mon1 (dMon1), a protein involve in Rab conversion regulates Dendritic Arborization. Knockdown of Mon1 increases branching of Type IV da neurons while overexpression decreases branching. In Type IV neurons Mon1 appears to interact with Rab5 and Rab7 suggesting a role for endocytosis in remodeling of these neurons. Mon1 also appears to regulate self-avoidance and tiling of dendrites. Our data further emphasizes the important role for endocytosis and trafficking in patterning of da neurons.

2.33 Sonali Salvi

Long-lasting behavioral effects of chemogenetic activation of cortical excitatory neurons in postnatal life

Work done on multiple rodent models has established that an early life stressor potentially has maladaptive eects on the animal's physiology and behaviour. The rationale being that the first few weeks after birth, mark a critical period wherein the circuits develop and they are particularly sensitive towards stimuli from the environment. In the early life model of maternal separation and postnatal fluoxetine, the animals show increased anxiety in adulthood in addition to enhanced serotonin 2A (5-HT2A) function in the pyramidal cells of medial prefrontal cortex in the maternal separation model. Moreover, pharmacological blockade and genetic studies of 5-HT1A and 5-HT2A point towards the involvement of these receptors in regulating mood related behaviour. These receptors are coupled to Gq or Gi G protein via which they carry out the downstream signalling. Hence, we hypothesised that the balance between the downstream Gq/Gi signalling instead of only a certain class of GPCRs being modulated might be a key player in determining behaviour. Here we use a chemogenetic approach (DREADDs) to study the implications of altering the cortical Gq/Gi signalling in excitatory neurons across different time spans in the organism's life and looking at its effects on mood related behaviour. We find that, animals show increased anxiety like behaviour in adulthood if the balance is tipped towards Gq signalling in the forebrain during the developmental stage whereas carrying out the same perturbation in adulthood has no effect on anxiety like behaviour.

2.34 Sravanthi Nadiminti

Investigating novel regulators of synaptic vesicle transport

Synaptic vesicle proteins (SVPs) are transported from Golgi complex to synapse in precursors vesicle compartments (pre-SVs). Exit of pre-SVs from cell body depends on microtubule anterograde motor UNC-104/Kinesin-3 (Hall and Hedgecock, 1991). Mutations in UNC-104 cargo binding domain causes SVPs to get stuck in the cell body (Kumar et al., 2010) demonstrating that recruitment of UNC-104 is a bottleneck in SVP transport. To identify molecules involved in UNC-104 dependent exit from cell body, we assessed genetic modifiers of unc-104 cargo binding defective allele, unc-104(e1265tb120). Here, we are presenting characterisation of tb217, an enhancer of und-104(e1265tb120).

2.35 Sreeja Kumari Dhanya

Investigating the role of STIM1 and Store-Operated Calcium Entry in Mouse Purkinje Neurons

Calcium ions are a universal second messenger that regulate various processes, such as proliferation, gene transcription, contraction, exocytosis, apoptosis, the immune response, and neurotransmission. Store-Operated Calcium Entry (SOCE) is a major mechanism for calcium mobilizationin in many non-excitable and some excitable cells. Store-operated channels (SOCs) open in response to depletion of calcium in the endoplasmic reticulum (ER) after stimulation of cell surface receptors coupled to G-proteins and tyrosine kinases. Store-operated channels (SOCs) consists of the pore-forming Orai proteins that are activated by the ER Calcium sensor STIM (stromal interaction molecule).

In the mature brain, store-operated Ca2+ entry (SOCE) is thought to be required for the maintenance of neuronal calcium homeostasis, which in turn can influence synaptic transmission and plasticity. However, the status of SOCE through STIM/Orai activation and its relevance to mammalian cerebellar neuron function are not well studied. Studies have proposed that deranged calcium signalling cascade in cerebellar Purkinje neurons might leads to neuronal degeneration and Spinocerebellar Ataxia (SCA)(Tada et al., 2014) . It has been found that mGluR1-dependent synaptic potentials and IP3R-dependent Ca2+ signalsare strongly attenuated in the absence of STIM1 in Purkinje neurons of STIM1 knock out mice(Hartmann J et al., 2014).These STIM1 knock out mice exhibit impaired motor learning and cerebellar motor deficits, but the molecular mechanisms explaining the deficits is not well understood. We have used Mouse Purkinje neurons as a mammalian model system to understand how STIM1 modulate neuronal function and how altered function of STIM1 leads to neurodegeneration.

References:
1) Tada M, Nishizawa M and Onodera O (2014) IP3 Receptors in NeurodegenerativeDisorders: Spinocerebellar Ataxias and Huntington's and Alzheimer's Diseases. Pathologies of Calcium Channels, DOI: 10.1007/978-3-642-40282-1_28.
2) Hartmann J, Karl R, Alexander R, Adelsberger H, Brill M (2014) STIM1 Controls Neuronal Ca2+ Signaling, mGluR1-Dependent Synaptic Transmission, and Cerebellar Motor Behavior. Neuron 82, 635–644.

2.36 Sreenath R

Studying the role of proteostasis of actin modulators in dendritic growth

Dendrite morphogenesis is a critical step in neurodevelopment where the basic architecture of the cellular computational machinery of a neuron is laid out. It is known that various external cues like trophic factors influence dendrite growth; and actin cytoskeletal rearrangement is indispensable to bring about these effects. In other neuronal compartments like axonal growth cones and mature dendritic spines, it has been shown that many proteins involved in actin dynamics are subjected to protein synthesis regulation in response to external cues. But it is not known whether growing dendrites employ similar mechanism of translational regulation, and which candidate proteins are involved. We hypothesized that actin modulator proteins could be undergoing translational regulation in growing dendrites and examined the translational profile of potential candidates in immature neurons in culture.

We identified some of the candidate mRNAs whose translation is upregulated on treatment with trophic factor BDNF. We found thatactivity of a key actin binding protein cofilin- was affected by BDNF in a translation dependent manner. Our imaging experiments show that these activity changes are somato-dendritic and not axonal. Our data further suggests that cofilin activity is a key juncture in actin rearrangement and is regulated by translation/degradation balance of its regulators. We are currently exploring what this could mean physiologically in the context of dendritic growth.

2.37 Sriram Narayanan

Activation profiles of Purkinje neurons during optomotor adaptation in larval zebrafish

It is believed that the cerebellum acquires and stores models of sensorimotor transformations. How these models are acquired and modified by learning is not clearly understood. Using the larval zebrafish as a model, we are working towards understanding how the cerebellar circuitry refines sensorimotor transformations to minimize errors in motor output. We use a custom designed closed-loop behavior setup to engage larval zebrafish in an optomotor adaptation task. In this task, head-restrained zebrafish larvae are placed in a virtual environment that provides optic flow. Tail movements made by the fish are detected in real time and transformed to forward displacement in the virtual environment. When feedback gain of this closed-loop environment is changed, the fish modulate motor output to compensate for sensorimotor mismatches introduced by the gain change. Using this behavioral paradigm, we have currently identified two distinct modes of motor adaptation that occur at different timescales. A fast mechanism, that enables fish to correct for gain changes within a swim bout and a slow mechanism that builds up over several bouts. After adapting to the new gain, fish showed consistent changes in bout velocity, duration and inter-bout interval, indicating that they had acquired novel sensorimotor transformations.To investigate the neural basis of these sensorimotor transformations, we imaged activity in specific cerebellar cell types during motor adaptation. We find both motor and sensory components in the activity profiles of Purkinje cells. We are now looking at how these activity profiles are modulated with respect to the specific kinematic changes observed during motor adaptation. Preliminary analysis shows distinct gain related activity in Purkinje cells.

2.38 Surbhi Dhingra

Structural Insights into Heteromeric Kainate Receptor Functions

Ionotropic glutamate receptors (iGluRs) are ligand-gated, cation channels. They are crucial for excitatory synaptic transmission and synaptogenesis in human brain. Functional iGluRs are predominantly hetero-tetrameric assemblies, each subunit consisting of an extracellular amino-terminal domain (ATD) and ligand-binding domain (LBD), a transmembrane domain (TMD), and a cytoplasmic carboxy-terminal domain (CTD). Kainate receptor subfamily plays important roles in both pre- and post-synaptic neurons and malfunctioning has been implicated in neurological disorders like schizophrenia, epilepsy etc. This project focuses on understanding the kainate receptor functions based on the structural and molecular insights. Presence of several splice forms of the receptor subunits and difficulties in expression in heterologous system requires rigorous construct optimizations. Hence, till date, no structure for the heterotetrameric assembly of these receptors has been reported. We have now optimized the constructs for GluK2/GluK5 (most abundant kainate receptors in vivo). We are able to overexpress and purify the functional receptors by baculovirus co-infected mammalian cells. Protein shows homogenous tetramer in biophysical analysis. The protein has been taken up for negative staining and cryo-EM optimizations. This study would elucidate how GluK5 regulates various properties of kainate receptors and how disruption in this regulation could lead to neuronal disorders.

2.39 Toshali Banerjee

DREADD-mediated activation of adult hippocampal progenitors: effects on neurogenesis and behavior

Adult-neurogenesis is a process of generating new functional neurons from adult neural precursors. It recapitulates the complete process of neuronal development of the embryonic stages. Active neurogenesis is spatially restricted to specifc "neurogenic" brain regions. One such region is the sub-granular zone (SGZ) in the dentate gyrus (DG) of hippocampus. More than 50% of adult-born DG neurons die before reaching the mature "functionally-relevant" stage. Certain factors such as environmental enrichment, voluntary exercise and learning have been shown to enhance neurogenesis. Although much has been learned about identities and properties of cell subtypes, supporting local environment and sequential steps of adult neurogenesis, we still have limited information on the functional impact of new neurons on the existing hippocampal circuitry and their contributions to the brain functions. In this study we attempt to activate adult-born hippocampal precursor cells directly using DREADDS (Designer Receptors Exclusively Activated by Designer Drugs) and investigate the consequences on behavioral and physiological outcomes.