Abstracts - BRAINY DAYS 3 - 18-20/6/2019

Tuesday, June 18

How gravity shapes the neural representation of complex space

Kate Jeffery, University College London

Studies of the neural representation of space in rodents traversing simple, horizontally aligned laboratory environments have uncovered a network of brain areas that encode location (place cells), heading direction (head direction cells) and distance travelled (grid cells). However the real world is three dimensional, having hills and valleys, and in some cases offering the possibility for free movement in any direction and in any posture. This talk will look at the theoretical implications of this additional dimension, and present some neural data investigating how the spatial coding neurons react in non-horizontal space. Our conclusion is that the spatial map emerges form an interaction between two reference frames - the locomotor plane (the surface the animal is on) and the gravity vector.

Voltage imaging and optogenetics reveal behavior dependent changes in hippocampal dynamics

Yoav Adam, Harvard University

A technology to record membrane potential from multiple neurons, simultaneously, in behaving animals will have a transformative impact on neuroscience research. Genetically encoded voltage indicators are a promising tool for these purposes, but were so far limited to single-cell recordings with marginal signal to noise ratio (SNR) in vivo. We developed improved near infrared voltage indicators, high speed microscopes and targeted gene expression schemes which enabled recordings of supra- and subthreshold voltage dynamics from multiple neurons simultaneously in mouse hippocampus, in vivo. The reporters revealed sub-cellular details of back-propagating action potentials and correlations in sub-threshold voltage between multiple cells. In combination with optogenetic stimulation, the reporters revealed brain state-dependent changes in neuronal excitability, reflecting the interplay of excitatory and inhibitory synaptic inputs. These tools open the possibility for detailed explorations of network dynamics in the context of behavior

An alternative view of what neural circuits may be doing

Christian Machens, Champalimaud Centre for the Unknown

The classical picture of a neural network assumes that each neuron sums its inputs, followed by a nonlinear activation function. Interesting computations emerge by combining and wiring up these individual units. While immensely successful (both in neuroscience and AI), this view has also created several persistent puzzles about the organization of neural systems. One puzzle are spikes, which have largely remained a nuisance, rather than a feature of neural systems. Another puzzle is robustness to perturbations, which is ubiquitous in biology, but

largely ignored in neural network modeling. I will show that these puzzles can be resolved if we shift our perspective of how neural systems operate. Based on only two assumptions - that the effective output of a neural network can be extracted via linear readouts, and that each neuron only fires to bound an error on this output, I will show how to derive a spiking network of integrate-and-fire neurons that exhibits irregular and asynchronous spike trains, balance of excitatory and inhibitory currents, and robustness to perturbations. I will provide geometric intuitions for the network's functionality, and use these insights to show how these networks can control the precision of their output via bottom-up and top-down gain modulation, even though they consist of integrate-and-fire neurons only.

Stable memory with unstable synapses

Omri Barak, Technion

What is the physiological basis of long-term memory? The prevailing view in neuroscience attributes changes in synaptic efficacy to memory acquisition. This view implies that stable memories correspond to stable connectivity patterns.
However, an increasing body of experimental evidence points to significant, activity-independent dynamics in synaptic strengths. Motivated by these observations, we explore the possibility of memory storage within a global component of network connectivity, while individual connections fluctuate. We find that homeostatic stabilization of network activity differentially affects different aspects of network connectivity. As a consequence, memory representations are stored as time-varying attractors in neural state-space and support associative retrieval of learned information. Our results suggest a link between the properties of learning rules and those of network-level memory representations and point at measurable signatures to be sought in experimental data.

Autism and sex differences

Simon Baron-Cohen, University of Cambridge

Multiple studies now show that in the general population, females on average show higher levels of empathy and males on average show a stronger drive to systemize. Empathy involves both a cognitive element (recognizing another person's mental state) and an affective element (responding to another person's mental state with an appropriate emotion). Systemizing is the drive to analyse or build systems (whether these are mechanical, mathematical, musical, natural, abstract, motoric, or collectible). Systems are anything that follows if-and-then rules. I present evidence that autistic people score below average on different measures of cognitive empathy and that they are intact and even sometimes superior on measures of systemizing. If one takes the difference (D scores) between one's scores on empathy and on systemizing then autism can be viewed as an extreme of the typical male brain. Autism is strongly genetic and is diagnosed more often in males than females. This is likely to be true even after taking into account under-diagnosis of females. One candidate biological epigenetic mechanism that might influence typical sex differences and may play a role in 'masculinizing' the autistic brain is prenatal sex steroid hormones, that shape brain development, and which themselves are under genetic control. I summarize work from our lab testing whether levels of prenatal sex steroid

hormones such as testosterone and estrogen are associated with typical sex differences in empathy and systemizing, and with autism and autistic traits.

Perceptual bias reveals slow-updating in autism and fast-forgetting in dyslexia

Merav Ahissar, The Hebrew University

Individuals with autism and individuals with dyslexia both show reduced use of previous sensory information (stimuli statistics) in perceptual tasks, even though these are very different neurodevelopmental disorders. To better understand how past sensory information influences the perceptual experience in these disorders, we first investigated the trial-by-trial performance of neurotypical participants in a serial discrimination task. Neurotypical participants overweighted recent stimuli, revealing fast updating of internal sensory models, which is adaptive in changing environments. They also weighted the detailed stimuli distribution inferred by longer-term accumulation of stimuli statistics, which is adaptive in stable environments. Compared to neurotypical participants, individuals with dyslexia weighted earlier stimuli less heavily, whereas individuals with autism spectrum disorder weighted recent stimuli less heavily. Investigating the dynamics of perceptual inference reveals that individuals with dyslexia rely more on information about the immediate past, whereas perception in individuals with autism is dominated by longer-term statistics.

Learning to predict: The facilitative effect of entropy reduction on language learning

Inbal Arnon, The Hebrew University

Understanding how children learn to talk is (still) one of the most puzzling questions in cognitive science. In my work, I explore experience-based explanations for how children learn language, and why they seem better at it than adults. In the current talk, I focus on the impact of a particular aspect of children's linguistic environment on their learning. During their first year, infants learn how to segment speech, extract words, and start mapping them to objects. Both the words they hear, and the objects they see are structured in a particular way: words in language follow a Zipfian distribution with few very frequent words and many low frequency ones. In contrast, most lab-based investigations of word learning and segmentation present learners with uniform distributions, where all words (and objects) appear equally often, and are therefore less predictable than the ones children are naturally exposed to. Still, relatively little work has explored the impact of entropy on language learning. In a series of studies, we now investigated the entropy of words in actual language and found that both children and adults show improved learning of a range of linguistic relations (segmentation, object-label pairings) when exposed to distributions that are more similar to natural language in their entropy values. I discuss the theoretical and methodological implications of these results for lab-based studies of language learning, and their possible impact on the way languages are structured.

The encoding of speech sounds in the human Wernicke's area

Edward Chang, University of California San Francisco

The human superior temporal gyrus (STG) is critical for extracting meaningful linguistic features from speech input. Local neural populations are tuned to acoustic-phonetic features of all consonants and vowels, and to dynamic spectral cues for intonational pitch. These local populations are embedded throughout broader functional zones that are sensitive to amplitude-based temporal cues that give rise to features of speech rhythm. Beyond speech features, STG representations are strongly modulated by learned knowledge and perceptual goals. Currently, a major challenge is to understand how these features are integrated across space and time in the brain during natural speech comprehension.

Wednesday, June 19

The amygdala and memory: recalling the past, imaging the future

Sheena Josselyn, University of Toronto

A fundamental goal of neuroscience is to understand how information is encoded and stored in the brain. The physical or functional representation of a memory (the memory trace or "engram") is thought to be sparsely encoded over a distributed memory network. However, identifying the precise neurons which make up a memory trace has challenged for scientists since Karl Lashley's "search for the engram" in the 1950's (Josselyn, 2015; Lashley, 1950; Josselyn, 2010; Josselyn et al., 2015). Moreover, it was not known why one neuron (rather than its neighbour) was involved in a given memory trace. We previously showed that lateral amygdala (LA) neurons with increased levels of the transcription factor CREB (cAMP/Ca ++ Responsive Element Binding protein), are preferentially activated by fear memory expression, suggesting they are selectively recruited into the memory trace (Han et al., 2007). We, and others, went on to show that these neurons were critical components of the memory network by selectively ablating (Han et al., 2009) or inactivating them (Zhou et al., 2009). These findings established a causal link between a specific neuronal subpopulation and memory expression, thereby identifying critical neurons within the memory trace. Furthermore, these results suggest that at least within the LA, eligible neurons compete for inclusion in a memory trace, and that the winners of this competition are determined by relative CREB function. Although competition between neurons, axons and synapses is necessary for refining neural circuits in development, little is known about competition between neurons in the adult brain. Our recent results suggest that this neuronal competition during memory formation limits the overall size of the memory trace (number of "winning" neurons) and is a mechanism that links (or disambiguates) related memories in the LA (Rashid, et al., 2016).
Memory impairments are a hallmark of aging, major mental illnesses (e.g., schizophrenia and depression) as well as neurological disorders (e.g., Alzheimer's and Parkinson's diseases). Therefore, understanding how the brain encodes and stores information is highly relevant to both mental health and mental

Surprising roles for astrocytes in plasticity and memory

Inbal Goshen, The Hebrew University

In addition to their well characterized supportive and homeostatic roles, pioneering studies have shown that astrocytes directly affect neuronal activity, supporting the concept of a "tripartite synapse", in which the astrocytes sense and actively modulate synaptic activity and plasticity. In recent years, groundbreaking research revealed many surprising roles for astrocytes in modulating neuronal activity and even behavior.

To directly and specifically modulate astrocytic activity we employed a chemogenetic approach: We expressed the Gq-coupled designer receptor hM3Dq or the Gi-coupled designer receptor hM4Di in astrocytes, which allowed their time-restricted activation or inhibition (respectively) by the application of the designer drug clozapine-N-oxide (CNO).

We discovered that astrocytic activation is not only necessary for synaptic plasticity, but also sufficient to induce NMDA-dependent *de-novo* long term potentiation in the hippocampus, which persisted after astrocytic activation ceased. In-vivo, astrocytic activation enhanced memory allocation, i.e. it increased neuronal activity in a *task-specific* way, only when coupled with learning but not in home-caged mice. Furthermore, astrocytic activation using either chemogenetic or optogenetic tools during acquisition resulted in memory recall enhancement on the following day. Conversely, directly increasing neuronal activity resulted in dramatic memory impairment.

Astrocytic inhibition during memory acquisition impairs remote, but not recent, recall. We show that this effect is mediated by a specific disrupting of the projection from the hippocampus to the anterior cingulate cortex by astrocytes.

I light of these activity-dependent and projection-specific effects of astrocytes on neuronal function, I will describe new research directions studying the geography and functional significance of hippocampal astrocytic domains, in clear brains and in the CA1 of behaving mice.

Behavioural signatures of a developing neural code

Lilach Avitan, The Hebrew University

During early life the neural code must develop to appropriately transform sensory inputs into behavioural outputs. However little is known about how developments in neural representations directly impact behaviour. To address this we used 2-photon calcium imaging of GCaMP6s zebrafish larvae and behavioural imaging of their hunting episodes at different ages. We showed behaviourally a spatial shift in prey detection in the visual field during early life, which is mirrored by a developmental shift in the locus of neural activity in the optic tectum. Decoding of spatial position from tectal activity improved with age at different rates across the tectum, and could predict individual differences in prey-capture behaviour. The dimensionality of evoked activity was higher than that of spontaneous activity, and some statistics of evoked activity became more distinct from those of spontaneous activity with age. Together these results show that developmental signatures of an emerging neural code can be directly related to observable properties of behaviour.

Sliders & Dragons: reptilian model systems for exploring cortical computation

Mark Shein-Idelson, Tel-Aviv University

Throughout the history of neuroscience, a large set of model systems has been used for studying a large variety of neuro-physiological questions. These model systems were frequently chosen for their unique experimental advantages, but studying them also provided a wider perspective on basic questions: By examining the manifestation of a given biological phenomenon across different species, one could separate the salient or fundamental from the transient or variable. In my talk I will focus on how studying reptilian forebrains can shed light on cortical computations and on the evolution of these computations. In particular, I will show what we can learn from studying turtles about the structure-function relations in neural circuits and what can lizard studies tell us about the organization of collective neuronal dynamics during sleep and across brain states.

Prefrontal circuits for cognitive control

Ofer Yizhar, Weizmann institute

The capacity to withhold a response when confronted with negative consequences is crucial for cognitive function, and is a hallmark of goal-directed behavior. The medial prefrontal cortex (mPFC) has been implicated in the regulation of impulsive behavior. However, the roles of distinct mPFC neuron populations in coordinating such behavioral responses remains unclear. We used the 5-choice serial reaction time task to investigate the roles of distinct mPFC projecting neuron populations in behavioral control. Silencing of the ventral mPFC caused an impairment in the ability of mice to adapt to changes in task structure, consistent with the crucial role of the mPFC in behavioral flexibility. To determine the contribution of distinct mPFC projections to behavioral performance in this task, we developed and validated a novel somatically-targeted anion-conducting channelrhodopsin (stGtACR2), allowing high-efficiency blue light-mediated optogenetic silencing. Inhibition of nucleus accumbens-projecting neurons in the mPFC using stGtACR2 led to reduced impulsivity, without altering performance or motivation. Our results establish the role of the mPFC and of frontostriatal projections in regulation of cognitive control.

Thursday June 20

Visualizing molecular events in synapse formation in vivo

Elly Nedivi, MIT

The introduction of two-photon microscopy for in vivo imaging has opened the door to chronic monitoring of individual neurons in the adult brain, and the study of structural plasticity mechanisms at a very fine scale. We have recently developed methods for labeling and chronic tracking of excitatory and inhibitory synapses across the dendritic arbors of L2/3 cortical pyramidal neurons in vivo, revealing a significant capacity for synaptic remodeling, even in the adult brain. The activity-regulated gene cpg15/neuritin has been previously implicated in stabilization and maturation of excitatory synapses. We combined multicolor two-photon microscopy with genetic and sensory manipulations to delineate, in vivo, steps in synapse formation and maturation, and examine sufficiency and requirement for activity and CPG15 at these defined steps.

Motor primitives in time and space by targeted gain modulation in recurrent cortical networks

Tim Vogels, University of Oxford

Animals perform an extraordinary variety of movements over many different time scales. To support this diversity, the motor cortex (M1) exhibits a similarly rich repertoire of activity. Although recent neuronal network models capture many qualitative aspects of M1 dynamics, such as complex multiphasic activity transients, they can generate only a few distinct movements. Additionally, it is unclear how M1 efficiently controls movements over a wide range of speeds and shapes. Here we demonstrate that simple modulation of neuronal input--output gains in recurrent network models with fixed connectivity can substantially and predictably affect downstream muscle outputs. Consistent with the observation of diffuse neuromodulatory projections to motor areas, our results suggest that a relatively small number of modulatory control units can provide sufficient flexibility to adjust high-dimensional network activity on behaviourally relevant time scales. Such modulatory gain patterns can be obtained through a simple reward-based learning rule. Novel movements can also be assembled from previously learned primitives, thereby facilitating fast acquisition of hitherto untrained muscle outputs. Moreover, we show that it is possible to separately change movement speed while preserving movement shape, thus enabling efficient and independent movement control in space and time. Our results provide a new perspective on the role of neuromodulatory systems in controlling recurrent cortical activity and suggests plasticity of single-neuron excitability as an important substrate of learning.

Non-invasive detection of age-related molecular profiles in the human brain.

Aviv Mezer, The Hebrew University

The biology of brain aging is yet to be fully characterized. It is currently unclear whether aging-related changes throughout the brain are driven by a common factor or result from a "mosaic" of several distinct molecular mechanisms. Magnetic resonance imaging (MRI) is the most widespread approach for non-invasive mapping of aging processes in the human brain. Quantitative MRI (qMRI) provides biophysical parametric measurements crucial for clinical and scientific studies. However, an important challenge in applying qMRI measurements is their biological specificity, as they change in response to both molecular composition and water content. Here, we present a novel approach that disentangles these two important biological quantities and allows to decode the molecular composition from the MRI signal. First, we demonstrated that our approach can reveal the molecular composition of lipids samples and allows to predict molecular histological measurements of the brain. Next, we uncovered multidimensional region-specific changes associated with the molecular composition of the aging human brain. Our novel method allowed to non-invasively disentangle the molecular alterations of the aging process from water-related changes. We found that in agreement with the "mosaic" theory, the molecular composition and the water content have distinct aging trajectories throughout the brain, which are also independent from the widely reported aging-related changes in volume and iron content. Our approach opens the door to a quantitative and specific characterization of the biological sources for the aging of different brain regions that until now was possible only post-mortem.

Bi-directional communication between the brain and the immune system

Asya Rolls, Technion

The philosophical mind-body problem examines the relationship between the mind, a mental process, and its impact on the body, a physical entity. Such interactions are manifested in modern medicine by the emergence of disease following stress, or recovery in response to placebo treatment. Nevertheless, this fundamental aspect of physiology remains largely unexplored. In this talk, I will focus on a specific aspect of brain-body interactions, the dialog between the brain and the immune system, the body's main protection mechanism. I will demonstrate mechanisms whereby these two systems can work in coordination, how the brain detects immune activity and how specific brain activity can orchestrate immune responses to cancer and gut inflammation.

Neural circuit mechanisms underlying cognition in rats

Carlos Brody, Princeton University

I will describe studies of the neural bases of cognitive processes. Rodents, mostly rats, are trained to perform behaviors that lend themselves to quantitative modeling that can help identify and assess specific cognitive processes, such as decision-making, short-term memory, planning, and executive control. With these well-quantified behaviors in hand, we then use electrophysiological

recordings, optogenetic perturbations, and computational modeling. We aim to understand the neural architecture underlying cognition, across multiple levels, from local neural circuits, to interactions between brain regions, to overall behavior. I will focus on decision-making and working memory. Gradual accumulation of evidence for or against different decision options has been proposed to be a core component of many different types of decision-making. I will describe our efforts over the past few years to identify the relative roles of cortical and subcortical regions in supporting this process.