

Talks abstracts

Plasticity and dynamics of neuron and astrocyte networks in visual cortex

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Feedforward and recurrent connections between excitatory neurons, combined with balanced inhibition, constitute a key network principle for creating response tuning in the cortex. Recent experiments from our laboratory demonstrate how such networks not only generate orientation selectivity in visual cortex but also mediate remarkable bottom-up and top-down plasticity even at the earliest stages of cortical processing.

The orientation preference of neurons changes systematically after short-term exposure to one stimulus orientation. Such reversible physiological shifts in orientation preference parallel the orientation tilt aftereffect observed psychophysically. The orientation change is caused by a decrease in response at the adapting orientation and an increase in response at a new preferred orientation that is shifted away from the adapting orientation. Thus, orientation plasticity is an active time-dependent process that involves both response depression and enhancement and likely involves intracortical interactions.

Orientation plasticity is seen primarily at specific foci in V1. V1 neurons are clustered according to their orientation preference in iso-orientation domains that converge at singularities or pinwheel centers. Neurons at or near pinwheel centers show pronounced changes in orientation preference after adaptation with an oriented stimulus, while neurons in iso-orientation domains show minimal changes. This difference in orientation plasticity is well explained by differences in local intracortical inputs to neurons at pinwheel centers and iso-orientation domains, as revealed by intracellular recordings and *in vivo* measurements of excitatory and inhibitory synaptic conductances.

A major puzzle in cortical physiology concerns the role of astrocytes, which constitute half the cells of the cerebral cortex. Using two-photon imaging in V1 of ferrets *in vivo*, combined with specific astrocyte markers, we show that astrocytes have well-defined visual responses and sharp tuning to visual stimulus features. Furthermore, their responses are mapped as exquisitely as those of adjacent neurons. Given recent evidence for a close apposition between neuronal synapses and astrocyte processes, we propose that astrocytes have a role in neuronal plasticity such as that induced by adaptation.

Neurons in V1 of alert, behaving monkeys also exhibit short-term orientation plasticity after very brief adaptation with an oriented stimulus, on the time scale of visual fixation. Adaptation with stimuli that are orthogonal to a neuron's preferred orientation does not alter the preferred orientation but sharpens orientation tuning. Thus, successive fixation on dissimilar image patches, as happens during natural vision, combined with mechanisms of rapid cortical plasticity, actually improves orientation discrimination.

Finally, natural vision involves judgements about where to look next, based on an internal model of the visual world. Experiments in behaving monkeys in which information about future stimulus locations can be acquired in one set of trials but not in another demonstrate that V1 neurons signal the acquisition of internal representations. Such Bayesian updating of responses based on statistical learning is fundamental for higher-level vision as well as for decisions about saccade target selection.

Cortical plasticity-based neurorehabilitation

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Studies of brain plasticity paralleling learning has provided an increasingly complete and detailed understanding of the change processes that underlie the acquisition of our skills and abilities as children, and that sustain and elaborate our abilities throughout our adult lives. After a brief discussion of the principles that govern plasticity in children and in adults, I shall briefly describe the development of, and the evaluation of brain plasticity-motivated behavioral strategies designed to ameliorate -- and to the extent possible reverse -- the neurological impairments associated with three common human conditions: impaired language development and dyslexia; functional losses accompanying normal and pathological aging; and schizophrenia and related psychotic illness.

Visual behavior and neural activity in the primary visual cortex in monkeys during natural vision

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In the visual cortex of cats and monkeys responses to stimuli placed in the cells' receptive field are modified by stimuli presented outside the "classical" field. Recent studies in monkeys exposed to complex visual stimuli that simulate natural viewing conditions have shown in addition that neurons in the primary visual cortex significantly reduce their firing when a larger portion of the visual field is covered with the sample image. These context dependent modulatory processes have been hypothesized to participate in stimulus selection, scene segmentation and perceptual grouping. However, little is known how these multiple modulatory influences are combined when animals are allowed to freely scan visual scenes and no data are available on changes of the oscillatory patterning and the synchronization of neuronal responses under such conditions. These data are of interest because it has been proposed that synchronization of neuronal responses on a millisecond time scale could serve to encode contextual information by defining relations between the features of visual objects. With free viewing, the relations between features that need to be grouped or segregated perceptually, change each time an eye movement is performed. Hence, the encoding of relations must occur at the same rate as the scanning of visual scenes.

We recorded simultaneously the discharges of neighboring neurons and local field potentials (LFPs) from the primary visual cortex of capuchin monkeys (*Cebus apella*) while they engage in free viewing of natural scenes.

We found that:

1. There is a time dependent modulation of neuronal activity in the cortex when animals freely examine natural images; this modulation depends on the type of eye movements. Saccades induce a time-dependent reduction of firing rate whereas visual fixations transiently increase the firing rate within a 50-210 ms time window.
2. In the absence of visual stimuli (dark), eye movements can still modulated firing rate.
3. Synchronous (< 5 msec time lag) neuronal activity was largely observed in the initial phases of the visual fixations while freely viewing natural scenes, and minimal during other eye movements.
4. Eye movements trigger significant changes in the frequency modulation of the local field potential in the primary visual cortex.
5. During free viewing of natural scenes, there is a substantial increase of beta and gamma band power peaking about 100 msec after the onset of the fixation, but absent in darkness. Also significant phase synchronization is observed at the same time lags.

In summary, synchronous firing as well as oscillations and phase synchronization in the beta and gamma frequency bands of the local field potentials, become predominant in the primary visual cortex during early periods of visual fixation but are absent during saccades, during eye drifts or without visual stimulation, and, thus, occur preferentially at times when new stimulus features need to be processed.

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The Processing of Tactile Information by the Hippocampus

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The ability to detect unusual events occurring in the environment is essential for survival. Several studies have pointed to the hippocampus as the key brain structure in novelty detection, a claim substantiated by its wide access to sensory information through the entorhinal cortex and also distinct aspects of its intrinsic circuitry. Though entorhinal input is sent to both the CA1 and CA3 hippocampal subfields, CA1 may be the place where novelty detection is actually implemented, by comparing the stream of sensory inputs it receives to the stored representation of spatiotemporal sequences in CA3. In some rodents, including the rat, the highly sensitive facial whiskers are responsible for providing accurate tactile information about nearby objects. Surprisingly however, not much is known about how inputs from the whiskers reach CA1 and how they are processed therein. Using concurrent multielectrode neuronal recordings and chemical inactivation in behaving rats, we show that trigeminal inputs from the whiskers reach the CA1 region through thalamic and cortical relays associated with discriminative touch. Ensembles of hippocampal neurons also carry precise information about stimulus identity, when recorded during performance in an aperture-discrimination task using the whiskers. We also

found broad similarities between tactile responses of trigeminal stations and the hippocampus during different vigilance states (wake and sleep). Taken together, our results show that tactile information associated with fine whisker discrimination is readily available to the hippocampus for dynamic updating of spatial maps.

Gustatory Processing is Rapid, Multisensory and Distributed

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Animals must make rapid decisions about whether to accept or ingest a particular food. By recording throughout the brain including the gustatory cortex, orbitofrontal cortex, amygdala and hypothalamus we will show that; that animals can learn to discriminate among tastants in a single lick (about 150 ms), there is sufficient information in a single lick for an animal to discriminate among tastants, and that when animals eat to satiety changes occur throughout the taste-reward pathways in a manner that is best characterized by populations rather than single neurons.

Interweaving in vitro and in vivo data for modeling the cortical column

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A first step in constructing an in silico model of a neocortical column is presented, focusing on the synaptic connection between layer 4 (L4) spiny neurons and layer 2/3 (L2/3) pyramidal cells in rat barrel cortex. The model is based firstly on a detailed morphological and functional characterization of synaptically-connected pairs of L4-L2/3 neurons from in vitro recordings and secondly on in vivo recordings of voltage responses of L2/3 pyramids to current pulses and to whisker deflection. In vitro data, combined with a detailed compartmental model of L2/3 cells, enable us to extract their specific membrane resistivity ($\sim 16,000 \text{ Wcm}^2$) and capacitance ($\sim 0.8 \mu\text{F/cm}^2$) as well as the spatial distribution of L4-L2/3 synaptic contacts. The peak conductance per L4 synaptic contact is $0.1 \text{ nS} - 0$.

Internal representations of sensorimotor learning and its implications for inference of reaching movements

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The talk describes our studies of internal representations of sensorimotor learning and its implications for inference of reaching movements from the electrical activity in the brain. First, we found that sensorimotor learning generates new neuronal representations and improves the information content about instructions and required actions by populations of motor cortex neurons. We then developed new algorithms to extract this information from local field potentials (LFP) and single unit activity. We use these algorithms as the core of brain machine interface that proves efficient in inferring arm movements from brain activity, even when the number of neurons is relatively small ($\sim 30-50$ cells) and even before the brain itself 'leans' to use the interface. These results shed light on the role of motor cortex in learning and contribute to the development of brain machine interface for clinical applications

Applications of implanted recurrent brain-computer interfaces

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An implanted recurrent brain-computer interface [R-BCI] consists of autonomously operating electronic circuitry, including a computer chip, that interacts continuously with the brain. We are investigating R-BCIs whose input is the activity of a motor cortex cell and whose output is electrical stimulation delivered back to the nervous system or muscles. Chronic implantation of the battery-powered R-BCI allows continuous operation and could permit the monkey to incorporate the artificial connection into normal behavior. Two applications of the R-BCI have therapeutic potential. First, the artificial recurrent connection can bridge impaired biological connections and allow the subject to learn to generate the neural activity that is

appropriate to compensate for the lost pathway. Second, by delivering stimuli synchronized with cell activity, continuous operation of the R-BCI can strengthen weak existing biological connections through Hebbian mechanisms. Preliminary results suggest that this experimental paradigm has numerous applications.

Humanoid Robotics Perspectives to Neuroscience

Gordon Cheng

ATR International, Kyoto, Japan/JST-ICORP, Saitama, Japan

In this talk we take the humanoid robotics perspectives to Neuroscience, in the studies of the brain. We will present a constructive approach in the exploration of Brain-like mechanisms. We place our investigations within real world contexts, as humans do. Three essential aspects motivate our approach: 1) In Engineering - Engineers can gain a great deal of understanding through the studies of biological systems, which can provide guiding principles for developing sophisticated and robust artificial systems; 2) Scientifically - Building a human-like machine and reproducing human-like behaviours can in turn teach us more about how humans deal with the world, and the plausible mechanisms involved; 3) Society - In turn we will gain genuine understanding towards the development of systems that can better interact with people and the environment.

Reverse Engineering, databasing and reconstructing biologically-constrained models of the mammalian brain

Henry Markram

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Technological innovation is increasing exponentially - the next 10 years will be equivalent to about 150 years of past research. This innovation is sweeping neuroscience into the industrial revolution to deliver data at a far greater rate than ever imagined. The global quest to reverse engineer the brain is now visibly increasing in speed and efficiency placing a heavy load on software and hardware solutions in neuroinformatics. The major lesson learned from the Human Brain Project's attempt to database the brain was not to build database without a common higher purpose. The higher purpose that has emerged and is a model! This is giving rise to a new generation of database systems, called "model-oriented databases." Such emergent databases can draw automatically from experimental and model databases to dynamically construct progressively higher level models to allow a form of "search by building" informatics. Neuroinformatics will finally need the most powerful supercomputers technology can provide to create dynamically emerging databases of computer models that can be used to explore through simulation, brain functions and dysfunctions. This evolvable approach provides an ideal framework to absorb the vast amount of data that has and will be produced as the reverse engineering of the brain approaches completion in the not too distant future.

L1-mediated somatic mosaicism in neuronal precursor cells

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Understanding what produces neuronal diversification has been a longstanding challenge for neuroscientists. The recent finding that LINE-1 (Long Interspersed Nucleotide Elements-1 or L1) retroelements are active in somatic neuronal progenitor cells provided an additional mechanism for neuronal diversification (Muotri et al Nature, 2005 and Muotri & Gage, Nature 2006). Together with their mutated relatives, retroelements sequences constitute 45% of the mammalian genome with L1 elements alone representing 20%. The fact that L1 can retrotranspose in a defined window of neuronal differentiation, changing the genetic information in single neurons in an arbitrary fashion, allows the brain to develop in distinctly different ways. This characteristic of variety and flexibility may contribute to the uniqueness of an individual brain. However, the extent of the impact of L1 on the neuronal genome is unknown. The characterization of somatic neuronal diversification will not only be relevant for the understanding of brain complexity and neuronal organization in mammals but may also shed

light on the differences in cognitive abilities, personality traits and many psychiatric conditions observed in humans.

Homeostatic functions of the central taste pathways

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The motivation to start or terminate a meal involves the continual updating of information on current metabolic status by gustatory and reward neural systems. It will be shown how populations of neurons located in different areas of the rodent brain can represent the animal's states of hunger/satiety across complete feeding cycles (hunger-satiety-hunger). In particular, these results support the hypothesis that while single neurons are preferentially responsive to variations in metabolic status, neural ensembles integrate the information provided by individual neurons to efficiently reflect behavioral states. It will also be discussed why this distributed code might constitute a neural mechanism underlying meal initiation under different metabolic environments.

Different molecular cascades in different sites of the brain are in charge of memory consolidation

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Memory consolidation of one-trial avoidance learning relies on a sequence of molecular events in the CA1 region of the hippocampus that closely resemble that of long-term potentiation (LTP) in that area. In addition, other molecular events, partly involving the same steps but with different timing and in different sequence in the basolateral amygdala, entorhinal, parietal and cingulate cortex are as important as those of the hippocampus for the consolidation of long-term memory (LTM). The biochemical changes that take place in CA1 and entorhinal cortex and are necessary for LTM consolidation are different from those that are required simultaneously for the formation of short-term memory (STM) lasting 1-6 h in these structures and others. The amygdala appears not to be involved in STM. In addition to STM, independently from it, and simultaneously with its first few seconds, an immediate memory system, possibly functioning as working memory operates in CA1, the basolateral amygdala and the prefrontal cortex. Its molecular mechanisms are different from those of STM or LTM.

Cerebellum-like Structures Yield Perspectives on Cerebellar Function

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The central nervous systems of most vertebrates include both a cerebellum and structures which are histologically similar to the cerebellum. The cerebellum-like structures are all sensory structures. They receive afferent input from the periphery in their deeper layers and parallel fiber input from other central structures in their more superficial molecular layers. The parallel fibers convey a rich variety of information from higher levels of the same sensory modality, from other sensory modalities, and from corollary discharges associated with motor commands. The parallel fibers of different cerebellum-like structures have been shown to generate predictions of expected sensory responses. Subtraction of these predictions allows unexpected sensory input to stand out more clearly.

The similarities in histological organization and in gene expression between the cerebellum and cerebellum-like structures are clear and suggest the possibility of common functions. We suggest that the climbing fiber input to the cerebellum is analogous to the peripheral sensory input to cerebellum-like structures and that the parallel fibers of the cerebellum generate predictions about the climbing fiber input that are used in various ways by the rest of the nervous system.

Neurochemical and Behavioral Alterations in Novel Genetic Models of Cholinergic Dysfunction

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The vesicular acetylcholine transporter (VACHT) is responsible for one of the most critical regulatory mechanisms of cholinergic transmission, the vesicular storage of acetylcholine. In order to understand the physiological roles of the VACHT and synaptic vesicle filling *in vivo* we generated several altered strains of mice with reduced expression of this transporter. Heterozygous and homozygous VACHT-knock-down mice have 45 and 65% decrease in VACHT protein expression, respectively. VACHT deficiency significantly affects ACh release both at the neuromuscular junction and in brain. Whereas VACHT homozygous mutant mice demonstrate major neuromuscular deficits, VACHT heterozygous mice appear normal in this respect and thus could be used for the analysis of central cholinergic function. Behavioral analyses of heterozygous VACHT deficient mice indicated that moderately (~30%) decreased central cholinergic tone strongly affects cognitive performance on several tasks. Most notably, social recognition memory is affected thereby revealing an important role for the cholinergic system in social interactions. These observations suggest a critical role of VACHT in the regulation of ACh filling of synaptic vesicles and physiological functions in the central nervous system and periphery. Our results suggest that even moderate declines of VACHT expression can affect behavior. Future experiments will be aimed to develop brain region specific KOs for the vesicular acetylcholine transporter to elucidate physiological functions of acetylcholine in the brain. Supported by NIH-FIC, FAPEMIG-PRONEX, CNPq and the Millennium Institutes.

The Use of Conformationally Sensitive Peptides in the Earlier Detection of Amyloid Proteins in Neurodegenerative Amyloid Diseases

**Alan S. Rudolph
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One of the hallmarks of many neurodegenerative diseases is the accumulation of misfolded amyloid proteins as plaques in the brain. These plaques are implicated in the cause of neurotoxicity and associated neurodegenerative symptoms including dementia and eventual death. Amyloid folding diseases include Alzheimer's disease (A β protein), Transmissible Spongiform Encephalopathy's (TSE) such as Creutzfeldt-Jacob and bovine mad cow disease (prion), Parkinson's disease (alpha synuclein), Huntington's chorea (Huntingtin protein) and other devastating disorders that vary by the type of amyloid protein. Adlyfe has developed an assay using these peptides for early diagnosis in blood and cerebrospinal fluid which will lead to more effective treatment of these neurodegenerative diseases. Our technology is based on PronucleonTM ligands that are small conformationally reactive peptides sequence-matched to a dynamic region on the misfolded amyloid protein target of interest. Upon interaction with the target, the ligands undergo an alpha helix to beta sheet conformational change matching the target state (beta sheet). This signal can be further amplified by recruiting additional Pronucleon ligands (through nucleation) to undergo a similar change which is easily detected by a spectral change in the engineered fluorophores on the peptides. These new conformationally reactive ligands are being developed as new biomarkers for the detection of specific amyloid forms relevant in disease. We have demonstrated the use of these peptides to monitor early events in amyloid protein accumulation in two neurodegenerative diseases. We have shown the utility of this assay in measuring β -sheet rich prion proteins in endemic TSE disease and in controlled models of infection in blood before symptoms occur. We have also measured specific A β proteins in biological fluids from Alzheimer's (AD) disease states. Post-mortem collected cerebrospinal fluid clinical samples from confirmed AD cases were distinguishable from age matched cognitively normal adults. The PronucleonTM peptides have also been shown to be directly recruited into growing A β fibrils and are currently being evaluated to screen for small molecules in a defined drug screening effort.

Molecular Taste Physiology of Tongue and Gut

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Significant progress has been made over the past few years in the identification of the molecular basics for taste perception, mainly with the discovery of a number of different taste receptors. With the exception of salty taste at least one dominant receptor has been identified for each modality such as sweet, sour, bitter and umami. For the known receptors and their modalities a clear picture is emerging of a labelled line at the periphery. Therefore, many recent studies address taste coding at the central level. However, it is obvious that events at the

periphery are not yet sufficiently understood to explain the difference in taste of a chicken versus a lobster.

At NRC we investigate the molecular physiology of different peripheral solute chemo sensory systems with special emphasis on the morphology of the cells involved and their sensitivity to cross-modality stimulation.

On the effect of retrieval in object recognition memory persistence

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Upon reactivation, consolidated memories are rendered vulnerable to metabolic blockers and become susceptible to the action of two different processes, namely extinction and reconsolidation, which affect subsequent retrieval in opposite ways. Thus, while extinction induces a progressive decline in the strength and/or in the probability of emission of the original response, reconsolidation would act not only to maintain but also to strengthen or update retrieved memories. During my presentation I will discuss about the biological and clinical implications of extinction and reconsolidation and show results suggesting that the fate of the retrieved trace depends on the length of the reactivation session and on the availability of salient and behaviorally relevant novel cues at the moment of memory retrieval.

Tauopathy caused by mutation of a novel E3 ubiquitin ligase

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A novel mouse neurological mutant, *lister*, was identified through a genome-wide ENU mutagenesis screen. Homozygous *lister* mice exhibit profound early-onset and progressive neurological and motor dysfunction. *lister* encodes a novel RING finger protein, LISTERIN, which functions as an E3 ubiquitin ligase. Although *lister* is ubiquitously expressed in all tissues, neurons and neuronal processes including motor and sensory neurons in the brainstem and spinal cord are primarily affected. Pathological signs include ubiquitin-positive aggregates, gliosis and dystrophic neuritis. Moreover, these mice exhibit accumulation of hyperphosphorylated tau, which is however in a soluble form, unlike the sarkosyl-insoluble phospho-tau aggregates found in Alzheimers' Disease (neurofibrillary tangles). Analysis with another *lister* allele generated through targeted gene trap insertion reveals that LISTERIN is required for embryonic development and confirms that direct perturbation of a LISTERIN-mediated pathway causes neurodegeneration. We are now utilizing a number of approaches to unravel LISTERIN's function and to understand how its mutation leads to disease, including by pursuing its critical ubiquitylation substrates. One of the hypotheses we are testing is that LISTERIN acts as an E3 for phospho-tau. In order to further evaluate the importance of tau for the mouse phenotype, we are also performing crosses between *lister* mice and *tau* knockout mice. Since the latter are essentially normal, the progeny of these crosses will allow us to determine the contribution of the loss of tau to the rate of progression of the *lister* disease. The *lister* mouse thus serves as a new model for understanding the molecular mechanisms underlying human neurodegenerative disorders.

The "dynamic association field" in visual cortical neurons: a possible fit between perception and action

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A prevailing concept in the role of thalamocortical pathways in sensory processing is the dominant influence of feedforward connectivity. In the case of the mammalian primary visual cortex (V1), the linear component of the neuronal input-output relationship seems to reflect the functional impact of the thalamic drive. It has long been known, however, that the classical discharge field of the cortical neuron is surrounded by a "silent" periphery (or non-classical receptive field (nCRF)), and combination of intracellular recordings and voltage sensitive dye imaging shows that the visual input arising from this surround results from the integration of activation waves spread over several mms within primary visual cortex. These findings, among others, have led to consider two linked possibilities: 1) the intrinsic cortical connectivity, through the recruitment of "horizontal" links as well as locally recurrent feedback, may remodel the

feedforward/thalamo-cortical processing of the visual image, and 2) the *effective* functional architecture of the cortical network is contextual, i.e. selected by the spatio-temporal statistics of the visual input.

This talk will review evidence from my lab, based on intracellular recordings of cortical cells, each submitted to different stimulation contexts (sparse noise, grating, natural scene, dense noise) in which the retinal effects of virtual eye-movements is, or is not, included. Results show that noise, efficiency and temporal precision of the spiking behaviour as well as reliability in membrane potential dynamics, all depend on visuomotor input statistics and that the neural code seems to be optimized for the viewing of natural scenes through natural eye-movement dynamics. These effects are best seen in full-field conditions, where centre-surround interaction dynamics endow cortical neurons with the ability to encode differentially local and global spatial information with low and high temporal precision, respectively. We propose that there exists for any V1 cortical cell a fit between the spatio-temporal organization of its subthreshold (nCRF) and spiking (CRF) receptive fields with the dynamic features of the retinal flow produced by specific classes of eye-movements (saccades and fixation).

This work has been supported by CNRS, ANR (Natstats), ACI-NIM and the European Community (FET- Bio-I3: 015879 (Facets)) grants to Y.F.

What connectivity inference can and can not tell us about brain function

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The recent years have seen heightened interest in the study of the dynamics of neuronal connectivity across levels of brain organization. One of main issue explored by investigators analyzing functional Magnetic Resonance Imaging (fMRI) or dealing with brain electrical activity measures has been the causal relationships between brain structures.

Technological advances in instrumentation allow for the monitoring of cortical activity at ever increasing spatial and temporal resolution. Novel multiple electrode techniques are now commonly used for the study of function of cortical areas. At a larger scale, data gathered from fMRI have also significantly improved the resolution in both time and space, but the results from recently proposed analyses methods have to be interpreted great care, since the current mathematical approaches hold strength and limitations as any statistical techniques. Other important issue is that any causality concept should be used adequately relying on precise definition and scope of its validity, which is strongly dependent on the mathematical or statistical model representing the biological neural system. I will discuss some issues of applicability of novel causality methods for studying and identifying connectivity in brain function, pointing their eventual strength and weakness.

The long-term future of LTP

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In this talk I will start by briefly reviewing the history of ideas relating to the neural basis of memory, and the background to the discovery of LTP in the hippocampus. I will then go on to discuss some of the still unresolved disputes concerning the cellular mechanisms responsible for the expression of LTP. Finally, I will suggest that a new approach is needed if the most important - and most intransigent - of the unresolved issues relating to LTP/LTD is to be solved: Do brains use LTP and LTD to store memories? I will argue that only by taking a network approach to testing the so-called "LTP=memory" hypothesis can we hope to achieve a compelling resolution, and I will make some suggestions about the sorts of experiment that might lead to such an outcome.

Dopamine transporter mutant mice in experimental neuroscience

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The monoaminergic neurotransmitter dopamine (DA) has been implicated in multiple brain disorders including schizophrenia, affective disorders, addiction and Parkinson's disease. Dopamine transporter (DAT) is a major regulator of both the intensity of extracellular dopamine (DA) signaling and presynaptic neuronal homeostasis. By deleting the gene encoding the DAT, a strain of mice lacking the mechanism to provide re-uptake of extracellular DA has been

developed. In DAT knockout mice (DAT-KO), extracellular levels of DA in the striatum are persistently increased 5-fold and this hyperdopaminergia manifests behaviorally as a pronounced locomotor hyperactivity. This hyperactivity is accompanied by specific perseverative patterns of locomotion and significant impairments in cognitive functions as well as sensorimotor gating mechanisms. Thus, DAT-KO mice may represent an animal model in which hyperdopaminergia related endophenotypes of some psychiatric disorders can be recapitulated, thereby providing test subjects for future treatment developments. Several pharmacological approaches to counteract consequences of increased central dopaminergic function have been tested in DAT-KO mice. Recently, these mice were used to develop a novel model of acute DA deficiency, creating the possibility to screen for drugs efficient in restoring locomotion in a DA-independent manner. Lack of DAT prevents recycling of released DA into the presynaptic terminal thereby resulting in a 20-fold depletion in intraneuronal storage of DA. The remaining DA is highly dependent on its *de novo* synthesis and pharmacological blockade of the DA synthesis in DAT-KO mice results in fast and effective disappearance of striatal DA. Dopamine-depleted DAT-KO mice (DDD mice) display striking behavioral phenotype including akinesia, rigidity and tremor reversible by L-DOPA and non-selective DA agonists. DDD mice represent a simple model of acute DA deficiency that can be used to screen for novel antiparkinsonian drugs. Furthermore, the ability to rapidly eliminate DA in DDD mice can serve as an effective *in vivo* approach to study modalities of neuronal activity and DA receptor signaling. This approach could be also highly valuable in studies aimed at further defining the role of DA in the neuronal circuitry involved in the motor control. Thus, DAT-KO and DDD mice provide a unique opportunity to create extreme levels of dopaminergic dysfunction *in vivo* and thereby can be used as valuable tools to understand role of DA in physiology and pathology.

Don't mess with the serotonin system during early brain development

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The midbrain raphe nuclear complex is well known to contain the largest complement of serotonergic neurons in the CNS and is the major source of serotonergic projections to the forebrain. In addition, serotonin (5-HT) has been postulated to play a trophic role in brain development and is also known to be one of the first neurotransmitters to appear in the CNS. Disruption of this system is considered to play a key role in the pathophysiology underlying a variety of mental disorders including anxiety, depression, sleep disorders, drug abuse, obsessive compulsive disorder, as well as autism. Despite treatment advances in the adult with selective serotonin re-uptake inhibitors (SSRIs), there is a major public health concern regarding the prescription of SSRIs to pregnant and nursing mothers as well as young children. The major motivation for our investigations is based on the fact that although SSRIs are the drug of choice for these patient populations, they may have adverse effects on the development of the immature brain. Recently, our laboratory and others have shown that neonatal treatments of rats with SSRIs resulted in: 1) a decreased expression of tryptophan hydroxylase (TPH) immunoreactivity, especially in the midline subregion of the raphe nuclear complex; 2) a reduction in the density and intensity of serotonin transporter immunoreactive fibers in the neocortex including medial prefrontal cortex, somatosensory cortex, and hippocampus; 3) abnormal barrel formation in the somatosensory cortex; and 4) specific changes in animal behaviors including increased locomotor activity and decreased sexual behavior. The functional implication and potentially harmful effects of SSRI treatment during early brain development will be presented and discussed.

Molecular analysis of the vocal control system of songbirds and other vocal learners

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The ability to learn how to vocalize is a rare trait among animals. Besides humans, where it represents the basis for speech acquisition and language development, vocal learning evolved only in cetaceans, possibly bats, and in three separate avian orders: songbirds, hummingbirds and parrots. Studies of activity-dependent inducible genes (particularly of *zenk* - a.k.a. *zif-268*, *egr-1* or *ngfi-a*), have allowed a detailed mapping and analysis of the brain areas involved in the control of vocal communication signals in these three avian orders. Such areas include auditory pathways, involved in the perceptual processing of vocalizations, a direct motor pathway, involved in the motor control of vocalizations, and an anterior "cortico"-striatal-thalamo-

“cortical” loop, involved in vocal learning and plasticity. Important novel insights into the functional organization and evolution of the avian vocal control system have resulted from: 1) the development of tools for functional genomics in songbirds (e.g. EST database, microarrays); 2) the imminent completion of the zebra finch genome sequence; 3) the identification of several markers representing neurochemical specializations of vocal control areas in songbirds and other vocal learners, and 4) a better understanding of the anatomical organization of the avian brain and its relationship to the brains of other vertebrate groups.

Mosaicism and aneuploidy in the human brain

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Neurons are notable for forming complex networks often consisting of hundreds of other cells and small changes in even a single neuron's genome could potentially alter the function of many others within an interconnected network. Recently we showed that both mouse and human brains contain cells that differ with respect to chromosome number manifested as aneuploidy (Rehen et al., 2001; Rehen et al, 2005). Analysis of neuroblasts undergoing mitosis detected lagging chromosomes, suggesting the normal generation of aneuploidy within the brain. Molecular karyotyping examination confirmed that approximately 33% of neural stem cells are aneuploid. Most cells lacked one chromosome, while others showed hyperploidy and/or trisomy. Interphase fluorescence *in situ* hybridization (FISH) showed that chromosome 21 aneuploid human neurons constitute approximately 4% of the estimated one trillion cells in the normal human brain. In comparison, human interphase lymphocytes present chromosome 21 aneuploidy rates of 0.6%. Together, these data demonstrate that the brain is a complex genetic mosaic of cells that can be distinguished based on their chromosomal complement. We propose that aneuploidy may imparts diversity and complexity to neuronal populations at the occasional expense of tumorigenesis or other diseases and that chromosome gain and loss may differentially affect neural differentiation of stem cells.

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Novel experience induces persistent sleep-dependent plasticity in the cortex but not in the hippocampus

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Episodic and spatial memories engage the hippocampus during acquisition but migrate to the cerebral cortex over time. We have recently proposed that the interplay between slow-wave sleep (SWS) and rapid-eye-movement (REM) sleep propagates recent synaptic changes from the hippocampus to the cortex. To test this theory, we jointly assessed extracellular neuronal activity and expression levels of plasticity-related immediate-early genes (IEG) *arc* and *zif-268* in rats exposed to novel spatio-tactile experience. Post-experience firing rate increases were strongest in SWS, and lasted much longer in the cortex (hours) than in the hippocampus (minutes). During REM sleep, firing rates showed strong temporal dependence across brain areas: Cortical activation during experience predicted hippocampal activity in the first post-experience hour, while hippocampal activation during experience predicted cortical activity in the third post-experience hour. Four hours after experience, IEG expression was specifically upregulated during REM sleep in the cortex, but not in the hippocampus. Cortical IEG expression was proportional to firing rates and to spindle-range oscillations typical of SWS-REM transitions. The results indicate that hippocampo-cortical activation during waking is ensued by multiple waves of cortical plasticity as full sleep cycles recur. The absence of equivalent changes in the hippocampus may explain its mnemonic disengagement over time.

