



## The Patterson Trust Postdoctoral Fellowship Program in Brain Circuitry

Bank of America, Trustee

### 2009 Recipients

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#### **Yashar Ahmadian Tehrani, Ph.D.**

Columbia University

"Quantifying the Importance of Precise Spike Timing in a Complete Retinal Population"

The role and importance of spike timing precision in the collective response of neuronal ensembles is one of the key questions in systems neuroscience. We seek to investigate this problem in a specific context: the network of parasol retinal ganglion cells of macaque retina. Several factors make this an ideal circuit in which to investigate the above questions. The response of this network is fast and temporally precise, and the ganglion cells exhibit significant synchrony in their activity. Yet the significance of these features for information encoding remains the subject of intense debate. This circuit also serves an important role in motion processing: it provides the main input to the magnocellular layers of the lateral geniculate nucleus, and these in turn comprise the main information channel to the motion-sensitive areas of the visual cortex.

Modern multi-electrode recordings from macaque retina provide us with complete access to the input and output of this network in a significant patch of the visual field. Our group has previously developed a powerful encoding model, fit to this data set, which accurately describes the full output of this circuit. Moreover, we have developed, for the first time, optimal Bayesian decoding methods that exploit this encoding model and are fast enough to allow for decoding of full spatiotemporal movies.

In this project, we will investigate how analytically perturbing these spike trains with single-spike resolution affects the optimal decoding of the experimentally recorded spike trains from this population. We will also make direct comparisons between this optimal performance and the behavior of human subjects in psychophysics experiments performed under identical stimulus conditions.

Using these methods, we plan to address the following key questions:

1. How precise is the retinal code? Are certain spikes more important than others, in the sense that perturbing these spikes has a larger impact on the decoded signal?
  2. Which collective perturbations have the greatest impact on this population neural code, and what information in these spike trains can we discard?
  3. What is the importance of precision in the behaviorally-relevant setting of velocity estimation?
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**Natalia De Marco Garcia, Ph.D., M.Sc.**

NYU Medical Center / NYU School of Medicine

"The Role of Neuronal Activity in the Assembly of GABAergic Interneuron Cortical Circuits"

A key feature of the central nervous system is its ability to process multimodal sensory information. The ensembles of neurons that permit the performance of such a challenging task are established during development. In the somatosensory cortex, GABAergic interneurons born in the ventral telencephalon undergo protracted migration to encounter their targets, the pyramidal cells, which originate in the dorsal telencephalon. However, the cellular and molecular mechanisms that regulate interneuron and pyramidal cell connectivity are poorly understood. In this proposal, I will investigate in vivo the role of neuronal activity in the establishment of interneuron morphology, laminar targeting and synapse formation. First, I will characterize interneuron-pyramidal cell connectivity at different developmental stages by combining the use of mouse genetics and in utero electroporation that will allow for selective labeling of these neuronal populations as they mature. Second, I will assess the impact of selectively manipulating neuronal activity in interneurons on the establishment of their connectivity. This study is anticipated to advance our knowledge of the cellular logic underlying circuit maturation. In addition, the project proposes a systematic approach for the visualization and manipulation of pyramidal cell-interneuron connectivity.

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**Soo Hyun Lee, Ph.D.**

NYU Medical Center / NYU School of Medicine

"Functional Analysis of Cholinergic Modulation of Cortical Circuitry"

Acetylcholine (ACh) is a crucial neuromodulator that mediates arousal, attention, learning and memory, and the processing of sensory information. Impairment of the cholinergic system is directly and broadly related to psychiatric and neurodegenerative disorders. The major source of acetylcholine to cortex originates from the basal forebrain (BF) with the nucleus basalis magnocellular (NB) constituting the principal source of cholinergic afferents to cortex. Projecting neurons from NB preferentially target GABAergic interneurons in cortex. Despite the importance of cholinergic modulation of cortical function, the detailed underlying neural circuitry is still largely unknown.

The central goal of this proposal is to determine the anatomical and functional specificity with which cholinergic projections target different classes of interneurons in cortex. Previous attempts at studying this circuitry, however, have been hampered by both the complex heterogeneity of NB projections to cortex and the diversity of GABAergic interneurons within cortex. To fully understand the modulatory effect of cholinergic afferents, it is critical to know how cholinergic afferent differentially engage the diverse subtypes of interneurons in cortex.

We will overcome this challenge by using photo-stimulation to control the activation of genetically targeted cholinergic neurons that express channelrhodopsin. Having isolated cholinergic projections to specific cortical interneuron classes, we will study their physiology using a combination of in vitro and in vivo techniques (Aim 1). We will use in vitro methods to ask whether the effect of acetylcholine on cortical activity differs as a function of interneuron cell type. Elucidating the mechanism by which ACh modulate cortical processing is critical to understanding the control of ongoing sensory processing. We will perform in vivo experiments to test the impact of ACh on sensory processing in

primary somatosensory cortex (Aim 2). In the proposed in vivo experiments, we will use ACh gain-of-function and loss-of-function approaches using genetically targeted cholinergic transgenic mice.

Combining in vivo and in vitro electrophysiology with genetic manipulation of the cholinergic system will allow us to investigate how cholinergic neuromodulation differentially impacts interneurons and shifts the degree to which different interneuron subtypes participate in sensory process in cortical circuitry.

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**Jiangteng Lu, Ph.D.**

Cold Spring Harbor Laboratory

"Role of a GABAergic Subnetwork in Critical Period Plasticity of Visual Cortex"

Neuronal circuits often display remarkable plasticity to sensory input especially during early postnatal life. For example, the closure of one eye during a critical period can permanently shift the response property of neurons in the primary visual cortex (V1) to favor inputs from the open eye – ocular dominance (OD) shift. Although much progress has been made in studying the anatomical, physiological and molecular components of OD plasticity, a comprehensive understanding that integrate these components in the context of relevant cortical circuitry remains a daunting challenge. Accumulating evidence suggests that proper function of GABAergic inhibitory neurons in V1 are critical to establish the physiological circuit architecture that allows OD plasticity to proceed. Indeed, deficiency in the GAD65 (isoform of GABA synthetic enzyme) abolishes OD plasticity, while activation of alpha1 subunit-containing GABAA receptors (alpha1-GABAARs) triggers OD plasticity. Recently, a subset of inhibitory neurons – Parvalbumin (Pv) positive basket cells – is suggested to be involved in OD plasticity. However, all evidences so far are correlative and inconclusive. The goal of my proposal is to directly examine the role of Pv interneuron network in OD plasticity, and to further investigate the underlying cellular and synaptic mechanisms, combining genetic manipulation and in vivo and in vitro electrophysiology. My host laboratory has recently established powerful genetic methods to label and manipulate specific GABAergic circuit in vivo, combining cell type-specific Cre knockin mice and Cre-activated viral gene expression. This allows me to specifically activate and inactivate the genetically defined elements in Pv cell circuits. I will directly manipulate GAD65 and GABA transmission from Pv cells and examine the effect on OD plasticity by in vivo single-unit recording. Furthermore, because Pv interneurons mediate inhibition through alpha1-GABAARs on both pyramidal neurons and other Pv interneurons, I will further dissect the role of these two components in OD plasticity by expressing shRNA-mediated alpha1-GABAAR in each cell types. This multidisciplinary approach offers an unprecedented opportunity to establish casual relationship between cellular-level activity and system-level neurophysiology. The completion of this proposal will yield fundamental insights into network mechanisms underlying cortical plasticity, and enrich our understanding of brain circuitry and function.

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**Ruchir Shah, Ph.D.**

New York University

"Input Specificity in Cortical Microcircuits"

The mouse prefrontal cortex (PFC) integrates inputs from multiple sources and controls many higher-order functions. Although advances in labeling and recording techniques have revealed the

organization of these inputs at the macro-circuit level, it remains unknown how different inputs are organized onto the dendrites of individual PFC neurons and if they have distinct functional properties. An understanding of functional input specificity at the sub-cellular level has important implications for synaptic integration and neuronal excitability, and may help explain the cellular mechanisms of PFC function.

In this proposal, we take advantage of recent advances in optical and genetic tools to examine input specificity in a cortical micro-circuit. We will express channelrhodopsin-2 (ChR2), a light-gated cationic channel, in the somatosensory cortex, hippocampus, or amygdala in order to selectively stimulate their axons using a blue laser beam. In addition, the use of 2-photon laser scanning microscopy (2PLSM) allows high resolution imaging and the ability to record calcium signals from individual dendritic spines evoked by these inputs.

Our first specific aim will test the hypothesis that different inputs are spatially segregated along the dendrites of layer 5 pyramidal neurons in the PFC. We will obtain patch-clamp recordings from these neurons while simultaneously activating ChR2-expressing axons. By positioning the laser beam at multiple dendritic locations and recording the electrical response at each location, we can create functional maps one input at a time. By comparing results from each input, we can determine if different modalities map onto distinct dendritic regions. Our second specific aim will test the hypothesis that these different inputs have unique functional properties of synaptic transmission. Using 2PLSM and ChR2 photoactivation, we will record spine calcium signals from identified inputs, examine postsynaptic properties, and determine the source of calcium.

Our results will provide novel insights into the principles of input specificity onto PFC neurons, and will determine whether differences in spatial segregation along dendrites are correlated with functional changes at dendritic spines. Importantly, these techniques can be applied to many different circuits where understanding the precise, sub-cellular organization of extrinsic inputs can yield a great deal of information about neural network function.

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**Babak Tahvildari, Ph.D.**

Yale University

"Functional Organization and Connectivity During Active Cortical Networks"

The cerebral cortex consists of a large sheet of highly interconnected neurons and networks. Far from being static, these interconnections are dynamically and rapidly regulated such that the functional interconnectivity of the cortex is constantly adjusting to the behavioral situation. The mechanisms by which the neocortex rapidly and dynamically changes its functional interconnectivity are only poorly understood. It has been proposed that neuronal network oscillations may be an important mechanism to support such a function. Indeed, previous results from our, and other, laboratories suggest that state changes in cortical network activity may rapidly control the functional connectivity of cortical networks. In this research proposal, we will investigate functional interconnectivity between different neural subtypes through the examination of the effects of spontaneous barrages of synaptic potentials, associated with the Up state of the slow oscillation in-vitro, using multiple whole cell recording and imaging techniques. Using different transgenic mouse lines expressing green fluorescent protein (GFP) in different subpopulations of local GABAergic inhibitory interneurons we will be able to examine the

interaction between putative excitatory and inhibitory cortical neurons and how this is modified by spontaneous recurrent network activity generated in the entorhinal cortical slice in-vitro. Specifically, we will test, using simultaneous multiple whole cell recording, 2-photon microscopy and Ca<sup>2+</sup> imaging techniques, how the activity of GABAergic neurons may modulate the responsiveness of other inhibitory interneurons and pyramidal cells, and in so doing how they contribute to local network function. In addition, we will also examine the balance of synaptic potentials arriving in identified local circuit GABAergic interneurons during the generation of recurrent network activity, since the mechanisms of synaptic control of these neurons during natural network activity has not yet been investigated. These studies will clarify the mechanisms by which the neocortex dynamically regulates its functional connectivity and excitability. This information is critical not only to our understanding of the basic, normal operation of the cerebral cortex, but also the dysfunctional properties of the cortex ranging from epilepsy to schizophrenia.

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**Marianna Yanike, Ph.D.**

Columbia University

"The Role of Caudate Circuitry in Categorical Decision-making"

In a dynamic environment behavior is constantly adjusted and requires selecting actions appropriate to a relevant context. The basal ganglia are important for adaptive decision-making and play a role in linking movement and cognition. Still little is known about neural circuitry underlying these cognitive processes. To study this, we propose to record from a group of caudate neurons in monkeys during a categorical decision-making task. Monkeys are trained to categorize speeds of random-dot patterns by making eye-movements to one of two spatial targets. They learn that one target is associated with 'slow' speeds and another target is associated with 'fast' speeds. Our preliminary findings show that caudate neurons respond to different events within this task and some caudate neurons encode category-specific information.

In this proposal we want to determine whether caudate local circuitry is functionally organized. The goal of this proposal is twofold. First, we will test whether caudate local circuitry is functionally organized (Specific Aim 1). We will characterize response patterns of populations of caudate neurons during the speed categorization task. This task allows us to separate neural activity related to movement, reward, and context/categorization. We will test whether an ensemble of caudate neurons share similar 1) saccade direction; 2) reward-related information (i.e. correct/error); 3) context/categorization specific responses. Second, we will determine connectivity in caudate circuitry (Specific Aim 2). The previous aim allows us to establish the functional organization of nearby caudate neurons. We hypothesize that this functional similarity of task-related responses will be stronger for interconnected cells as measured by higher spike count correlations. Also we will compare the timecourse and response patterns of neuronal activity of interconnected neurons by computing cross-correlation functions to test whether different types of caudate neurons have similar or complimentary task-related response properties.

The results of this study will not only allow us to generate novel conclusions about the role of the caudate nucleus in categorical decision making, but also will provide evidence for whether there is functional organization within caudate local circuitry. The present findings will also have implications for how caudate signals are interpreted by structures receiving caudate information.

## 2008 Recipients

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### **Albert Ayoub, Ph.D.**

Yale University

"Primitive Cortical Networks"

The cerebral cortex features functionally distinct cellular areas and complex circuitry responsible for higher brain functions, which if disturbed would result in brain malformations and cognitive impairment. Recent advances suggest that early specification in the telencephalon, as in the spinal cord, depend on intercellular signaling and not just diffusible molecules from distant patterning centers (Jessell, 2000; Gal et al., 2006). The intercellular signaling mechanisms operating in the early embryonic brain at or before the onset of neurogenesis are largely unknown. Accumulating evidence suggests that these signaling mechanisms are involved in the increase of radial units and the diversification of cells within these functional units (Rakic, 1988; Mallamaci and Stoykova, 2006). In this project, I propose to investigate events at or before the onset of cortical neurogenesis to uncover mechanisms necessary to establish primitive cortical networks upon which future brain circuitry is built. A new, previously undescribed, population of neurons is thought to migrate into the primitive cortex days before the onset of local neurogenesis in the early human embryos (Bystron et al., 2006). These "predecessor" neurons have complex branches and long trailing processes but no identifiable synaptic contacts. Local signaling may precede the formation of synapses and, therefore, be the initial mode of intercellular signaling leading to the formation of primitive circuitry and the diversification of the neural stem cells. The appearance of what we identified as the homologues of predecessor neurons at embryonic day 9.5 in the mouse telencephalon is concomitant with the expression of a poorly characterized GABA receptor subunit that we identified through a comparative genomic screen. This receptor subunit (and its isoforms) is highly conserved (96%) between humans and macaques but is only 70% homologous to the mouse isoform. Here we propose to study intercellular signaling between predecessor neurons and neuroepithelial cells in the mouse and monkey embryos. Our hypothesis is that predecessor neurons initiate the formation of primitive cortical networks through intercellular signaling with neuroepithelial cells. Therefore, I propose to use a comparative approach between early rhesus macaque and mouse embryos to perform (1) ontogenic characterization of predecessor neurons and (2) functional characterization of predecessor neurons. This project and the proposed experiments will build on the strengths of Dr. Rakic's laboratory in cortical development and provide me the opportunity to uncover molecular mechanisms responsible for the formation of the neocortex.

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### **Eugene Civillico, Ph.D.**

Princeton University

"Optical Analysis of Circuit-level Sensory Processing in the Cerebellum"

The intricate and regular anatomical structure of the cerebellar cortical circuit invites compelling theories of function; however, the nature of the computation performed by this circuit remains mysterious. Two-photon imaging allows us to observe local correlations in complex-spiking microbands of Purkinje cells. Microbands delineate a parasagittal organization of cerebellar responses

under both spontaneous and sensory-evoked conditions. We propose to investigate further the spatiotemporal structure of spontaneous and sensory-evoked activity in the cerebellar cortex of the anesthetized and alert mouse. We hypothesize that interneurons are able to encode the local density of parallel fiber and climbing fiber input, and use this information to selectively inhibit portions of Purkinje cell dendrites, introducing spatial heterogeneity into the Purkinje cell's calcium-based complex spike. In this way, local density of activity may allow dendritic responses to be not simply all-or-none, but also graded.

Specific Aim 1: We will record calcium transients from ensembles of cerebellar interneurons in order to characterize their participation in coordinated patterns of activity. We will make use of the known somatosensory-responding regions in crus I and II of the cerebellar cortex to drive the cells. The goal of these experiments will be to determine the spatial and temporal scales over which stellate and basket interneurons are correlated with one another and with neighboring Purkinje cell dendrites, whether these scales differ between evoked and spontaneous activity, and whether these correlations reflect the parasagittal synchrony of Purkinje cell dendrites.

Specific Aim 2: We will evoke complex spikes in Purkinje cells via a stimulating electrode in the contralateral inferior olive. We will activate parallel fibers with electrical and somatosensory stimuli to test whether stimulation of intersecting parallel fibers can fragment the Purkinje cell calcium transients.

Specific Aim 3: We will perform experiments similar to those described in Aims 1 and 2, using cortical EEG recordings to monitor the level of anesthesia, and eventually moving to experiments in the alert animal. The data obtained in this way will be invaluable to the interpretation not only of our previous data, but also the huge body of recordings in the literature from anesthetized animals.

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## **Demir Ebru, Ph.D.**

Cold Spring Harbor Laboratory

"Electrophysiological Investigations of Associative Olfactory Memory in *Drosophila*"

How does an animal learn which stimuli predict reward, and which predict punishment? The brain has a remarkable ability to link information from many different sensory modalities. Sensory information is represented in the brain by populations of co-active neurons. How associative learning creates links between these co-active populations of neurons is a fundamental question in understanding brain function.

Together with Dr. Glenn Turner at ColdSpring Harbor Laboratory, I plan to use a combination of genetics and in vivo electrophysiological recordings to address these questions in *Drosophila*, an excellent model system where olfactory learning and memory has been extensively studied with genetic and behavioral approaches. The available genetic tools in *Drosophila* will enable us to label defined populations of neurons, manipulate their activity, and misexpress/overexpress genes involved in learning. Thus, we will be able to determine how learning modifies olfactory representations in the brain.

The study here aims to investigate:

1) When a neuron represents many different stimuli, how is the specificity of associative memory achieved? (i.e.: which synapses change strength, and which ion channel properties change?)

2) How do olfactory representations change when an association is formed?

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**Theofanis Karayannis, M.Sc., D.Phil.**

New York University

"In vivo Labelling of Developing Interneuronal Cortical Networks"

The activity of cortical GABAergic neurons is crucial to a number of processes, ranging from brain development to their predominant role in inhibition of neuronal output in the mature brain. Epilepsy, autism and schizophrenia are all examples of disorders that may be caused by defects in cortical interneuron signalling. Understanding how the variety of interneuron subtypes differ in function during development but also in the fully developed brain, is today severely hampered by the lack of methods to label small cortical subcircuits related to a single type of interneuron. The proposed project aims at developing a novel virus-based method allowing for the in vivo labelling of all neurons connected to specific subclasses of cortical interneurons, in a temporally-inducible manner. The virus carries a deletion mutation that prohibits it from spreading more than one synaptic connection away and provides a hitherto unparalleled fluorescent signal. This will permit the analysis of the integration of interneuron subtypes into cortical microcircuits using morphology, electrophysiology and functional imaging. The specific aims of the project are:

- 1) To characterize the connectivity of specific cortical interneuron subtypes using molecular markers, anatomical location and morphology through the use of low titer infection of pseudo typed rabies virus, engineered to allow their primary afferent projection neurons to be determined.
- 2) To study the functional connectivity between cortical interneurons and their afferent and efferent partners using multi-pipette patch clamp recordings in combination with calcium imaging.

The methodology outlined above can be easily transferred to other neuronal systems, suggesting that success in this endeavour would constitute a major technical breakthrough in general neuroscience.

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**Romesh Kumbhani, Ph.D.**

New York University

"Spatiotemporal Dynamics of Pattern Motion in Area MT"

The visual cortex is responsible for creating an internal representation of the external world in order to guide appropriate behavioral responses. Creating this representation requires complex neural circuitry dedicated to computing various aspects of the visual world. The overall goal of the project is to understand how cortical circuits in area MT (V5), an extrastriate visual area specialized for the analysis of visual motion, transform their inputs to compute a representation of the coherent motion of visual patterns. This is the best-understood case of how cortico-cortical circuits propagate information, and our hope is that understanding it will help to develop and constrain a general model for cortical computation.

The specific goals of this proposal are designed to refine a model of MT processing recently developed in the Movshon laboratory. This model uses a "cascade" of linear-nonlinear stages to represent motion

computations in V1 and MT, but does not incorporate temporal and spatial dynamics. Previous work has shown that the responses of MT cells evolve over a period of 50-100 ms after response onset, and suggests that the computation of pattern motion involves several functional elements with different characteristic temporal signatures. Furthermore, recent evidence has suggested that the computation of pattern motion is performed locally (i.e., only inputs with spatially overlapped receptive fields are integrated by MT neurons to represent pattern motion). This project proposes several experiments intended to link these different mechanisms with the functional elements of our existing model. First, we aim to examine the integration properties of MT cells using temporally or spatially interleaved stimuli. Then we will analyze the evolution of pattern motion selectivity by evaluating the cascaded model of MT at multiple time points.

In combination, these sets of experiments will enrich our understanding of the computations involved in the analysis of visual pattern motion in area MT, as well as, enhance our understanding of the general computing architecture that links different areas of the cortex into the complex networks responsible for higher cognitive functions.

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**Duda Kvitsiani, Ph.D.**

Cold Spring Harbor Laboratory

"Neural Circuit Mechanisms for Prefrontal Persistent Activity and Reward Anticipation in Rodents"

A hallmark of higher brain function is the ability to predict outcomes and maintain these predictions over time in the service of guiding behavior. The neural substrate for maintaining information in "mind" is thought to be provided by the persistent firing of neurons in the absence of external cues. Indeed, such persistent neural activity is commonly observed in prefrontal cortex of both primates and rodents but little is known about the neural mechanisms for generating it. The overreaching goal of my proposal is to understand the neural circuit mechanisms underlying persistent activity in the prefrontal cortex of rodents and how it controls behavior. To study this I will take advantage of two recent developments: the ability activate genetically targetable neural cell-types with exogenous rhodopsins (ChR2 and NpHR) and recordings of persistent activity in rodent prefrontal cortex during reward anticipation. Specifically, I will use mouse molecular genetics to express ChR2 and NpHR in two morphologically and functionally distinct classes defined by Calcium binding proteins: Calretinin and Parvalbumin. This will allow me to specifically activate and inactivate these neurons/ *in vivo*/. Using these genetically engineered mice, I will perform behavioral electrophysiology to test the functional role of distinct populations of interneurons in the generation of persistent neural activity and also its behavioral impact. I will carry out the molecular genetics component of this project in Josh Huang's laboratory and the behavioral electrophysiology studies in Adam Kepecs's laboratory, both at CSHL. This multi-disciplinary approach presents an unparalleled opportunity for me to begin to outline a mechanistic explanation for higher cognitive functions in terms of neural circuitry.

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**Xin Li, Ph.D.**

New York University

"Neuronal Specification and Connectivity in the Drosophila Optic Lobes"

In the human brain, a great variety of neurons are connected in a complex neural network. How genetic programs specify this great variety of neurons and control their assembly into neural circuits is

still poorly understood. The *Drosophila* visual processing centers provide a simpler but powerful model system to study this question. Our long-term goal is to understand the color information-processing network in exquisite details. This project is focused on the first center for color information-processing, the medulla. The host lab has characterized most neuronal subtypes of the medulla based on their morphology, connectivity, and molecular markers. The majority of more than fifty subtypes of medulla neurons can be marked by one of three mutually exclusive enhancer trap lines (in the genes *dll*, *ey* and *ap*, which encode early expressed transcription factors), each marking a specific subset. I propose to perform a genetic screen, using ~4000 mutagenic piggyBac insertion lines, to identify genes required for neuronal specification and neural circuit assembly in the *Drosophila* medulla. The piggyBac insertions, which are all mapped to the genome, are on FRT chromosomes and were designed to be used in a MARCM (Mosaic Analysis with Repressible Cell Marker) approach to visualize individual homozygous mutant cells in a phenotypic wild type background. I will mark permanently specific subtypes of neurons with another marker (RFP driven by the promoter of *dll*, *ey* or *ap*), and examine if a mutation affects their final cell fate, morphology and connectivity. I will thus be able to identify genes acting downstream of these transcription factors. I will be looking for mutant neurons marked by both GFP and RFP with morphology different from each of the identified neuronal subtypes for the given RFP marker. As validation for the screen, I will first examine the effect of mutations in *dll*, *ey* and *ap* as well as the ectopic expression of these genes in wild type or cells mutant for another transcription factor. The morphology of cells mutant for each of the piggyBac lines will then be evaluated to identify genes whose function is required for specification and connectivity of medulla neurons.

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### **Hysell Oviedo, Ph.D.**

Cold Spring Harbor Laboratory

"Linking Structure and Function in the Auditory Cortex"

Linking structure with function has been the driving force behind efforts to understand the brain. As the number of tools designed to study brain function have grown, studies combining complementary approaches have become increasingly powerful. The auditory cortex is an example of a brain area that is little understood despite being studied for as long as visual cortex. Unlike the visual or barrel-whisker system, audition lacks an understanding of local microcircuitry, which could provide invaluable insights into computational implementation. One of the tools that helped to connect circuitry with computational output in the barrel and visual system is Laser Scanning Photostimulation (LSPS). This technique has been used to map functional connections between neuronal populations and their presynaptic inputs by inducing the photo-release of caged glutamate to probe connections. I recently began to apply this technique in the mouse auditory cortex and have uncovered patterns of synaptic organization unlike those observed in either the barrel or visual systems: the laminar flow of information does not resemble that described for the canonical cortical circuit and there is no classical columnar arrangement of synaptic inputs to neighboring cells. Another technique that has advanced our understanding of brain circuitry and function is the ability to label cells *in vivo* following the characterization of their response properties. Anatomical recovery of the labeled cell then provides for a morphological identification of the functionally characterized cell. This has been done routinely in the barrel and visual system, but has been underused in studies of auditory cortex. The goals of this proposal are twofold: to trace the flow of auditory information from the thalamus to the earliest stage of intracortical computations, and to use this circuit diagram to understand auditory response

properties in the intact animal. For the latter goal, I will use cell-attached recordings in vivo to characterize single cell responses to tones and deliver dyes to the cell for post-hoc identification. I will accomplish these aims using techniques I have acquired during my doctoral work (in vitro recordings) and following my more recent experience with in vivo recordings/labeling and LSPS.

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**Taro Toyozumi, Ph.D.**

Columbia University

"Understanding the Role of Activity Dependent Plasticity on the Development of Visual Circuits"

Children can often learn faster than adults on languages, sports, and music. Indeed, we know that there are specific periods of time, so-called critical periods (CPs), during which brain circuits are particularly susceptible to being changed by particular types of experience. It is important to understand the difference between the CP and the non-CPs, and to understand how critical periods are initiated.

A model system for understanding CP is ocular dominance plasticity: after monocular deprivation (MD; closure of one eye), input to primary visual cortex (V1) becomes dominated by the open eye. This occurs only during the CP. In mice, maturation of cortical inhibitory circuitry initiates this CP. Even before this CP, cortex is plastic: receptive fields retinotopically refine, and MD of the contralateral eye retards this refinement without changing the relative strength of the two eyes' responses.

In this project, activity dependent synaptic plasticity is modeled as a phenomenological learning rule for synaptic weights that has the Hebbian property that "neurons that fire together, wire together" and the homeostatic property that weights are rescaled to keep postsynaptic activity near some desired set point. I will study, with a modeling approach, how the maturation of inhibitory circuitry initiates the CP of OD plasticity, and how there can be activity-dependent plasticity without OD plasticity before the maturation of inhibition.

In cats, the onset of the CP for MD plasticity produces significant change in ocular dominance column structure. Responses in cat V1 early in development are dominated by the contralateral eye. Then, beginning approximately at the onset of the CP for MD plasticity, the inputs from the two eyes become roughly equalized and segregate into alternating ocular dominance columns. This equalization and segregation does not occur if the eyes are not opened, which prevents the maturation of inhibition and the opening of the CP. Hence the third aim of this proposal is to understand how the maturation of inhibition that initiated the CP can also change the circuit structure by equalizing the ocular dominance columns in cats.

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**Tim Vogels, Ph.D.**

Columbia University

"Seeing Synaptic Strength: A combined Two-Photon / Theoretical Study of the Function of Dendritic Spines"

Dendritic spines receive the vast majority of excitatory synaptic transmission but their role in the integration of presynaptic signals remains unknown. Spine morphology differs greatly between individual spines and the underlying functionality of this diversity has long been discussed. Both

chemical as well as electrical compartmentalization have been proposed as the major function of the spine. Recent work shows strong correlations between the amplitude of excitatory postsynaptic potentials (EPSP) and spine neck length as well as correlations between the EPSP and spine head volume. These findings suggest that it may be possible to extract the functional importance of a synapse from morphological data alone.

A combined approach of two-photon uncaging of glutamate, electrophysiology, and electron microscopy will allow me to establish a complete electro-morphological map of dendrites and spines. This will let me rigorously dissect the different morphological properties of spines and their respective effect on EPSP amplitude. In parallel, I will create a database of model spines to provide a theoretical foundation for my experiments, allowing me to express the dependencies of morphology and function in mathematical terms. This combination of theory and experiment will make it possible to predict ad hoc postsynaptic efficacies of entire dendritic trees based solely on light microscopy. Such a non-invasive method to probe the electrical properties of a neuronal network would be a break-through in the quest to unravel the functional architecture of the mammalian cortex, with implications for many fields of neuroscience.

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## 2007 Recipients

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### **Fatiha Boukhtouche, Ph.D.**

Columbia University Medical Center, New York

“Molecular Mechanisms of Synapse Elimination in the Mouse Cerebellum”

The function of the nervous system depends on precisely connected neuronal networks that are assembled during development. Circuit assembly encompasses a series of steps, culminating in the formation of synaptic connections. During postnatal development the initially pattern of connections is substantially refined by stabilization of some synapses and elimination of others. This project will focus on the molecular mechanisms of synapse elimination using the mouse olivocerebellar system as a model. This circuit controls the integration of sensory and motor information and is critical for motor planning and learning. Two major constituents of this circuit, Purkinje cells and climbing fibers (the axons of inferior olivary neurons) undergo extensive and well-defined synapse elimination. Therefore, they represent an ideal model to study the general mechanisms of this process.

Specifically, this proposal will focus on alpha-chimaerins, two isoforms of a cytoplasmic signaling molecule. Several observations from previous work in the laboratory support a potential relevance of alpha-chimaerins for synapse elimination: First, Purkinje cells and inferior olivary nucleus neurons each express a specific alpha-chimaerin isoform. Second, alpha1-chimaerin contributes to synapse elimination in vitro. Third, alpha2-chimaerin mutant mice show motor defects which are indicative of defects in cerebellar circuitry. We will use a combination of lentiviral gene transfer and mouse genetics to explore the functions of alpha-chimaerins in parallel and climbing fiber synapse elimination in vivo. Neuronal connectivity in the mutant mice will be analyzed using anatomical and electrophysiological methods.

The new insights gained in these studies should be valuable not only for advancing the general knowledge of synapse elimination and neuronal network formation during development but should also be relevant for the understanding of neuro-developmental disorders. Abnormal neuronal connectivity is thought to underlie the abnormalities in schizophrenia and autism. Defining the mechanisms of normal synapse formation and elimination during development will be instrumental for defining the cellular defects that underlie the neuronal connectivity defects in these disorders.

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**Dylan Clyne, Ph.D.**

Yale University School of Medicine, Connecticut  
“Neuronal Control of Courtship in *Drosophila*”

Nearly all animals display elaborate, instinctive courtship rituals. Divergence in these behaviors, particularly the mating songs in insects, are often the first step towards speciation. How do these distinct male and female behaviors emerge from the genetic differences that define the sex of an animal? By clarifying the relation between genes and neural circuits, this proposal can shed light on how the nervous system evolved and on how genetic variations predispose some people to specific mental illnesses (e.g. schizophrenia, epilepsy, etc.). *Drosophila* genetics has been tremendously successful in uncovering the genes that underlie sex-determination and sex-specific behaviors. In particular, sex-specific splicing of the fruitless (*fru*) gene has been shown to act as a master switch that determines whether a fly displays male or female courtship behaviors. FRU is expressed in approximately 3000 neurons (FRU neurons) that remarkably, share far more anatomical similarities than differences between males and females. Do a few differences in the male and female FRU circuit make all the difference? The physiological roles of FRU neurons are not well characterized, because most are inaccessible to traditional electrophysiology. This proposal overcomes these barriers by using light to activate highly specific groups of neurons that are genetically engineered to respond to illumination. The behaviors elicited by these artificial signals can then be linked to identified neuronal substrates. Using genetically targeted photostimulation, this proposal will characterize the contribution of specific FRU neurons to courtship song production and test the hypothesis that sex-specific splicing of FRU alters their physiological role in the courtship circuit.

AIM 1 Analyze acoustic structure of “fictive” song generation

AIM 2 Neuronal control of wing asymmetry and song elements

AIM 3 Characterize functional sex-differences, if any, in FRU song circuitry

AIM 4 Identify higher neural centers for song initiation and coordination

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**Ben Collins, Ph.D.**

New York University, New York

“Dissection of a Neuronal Circuit Controlling a Simple Circadian Behavior”

The circadian clock in the suprachiasmatic nucleus (SCN) links the internal body clock to the environment. The synchronization of the intracellular molecular clocks in individual clock neurons and their ability to co-ordinate complex behavioral and physiological processes depends on circuits between individual neurons. These circuits are built upon time-dependent regulation of neuronal

activity and neurotransmitter release from individual neurons. However, the complexity of the SCN (~20,000 neurons and multiple cell groups) makes it difficult to determine how clock neurons interact.

Here we propose a study of a much simpler neuronal circuit with only two circadian clock neuron groups and an easily quantifiable behavioral output. *Drosophila* larvae avoid light and this requires both the larval visual system and the cells it innervates – circadian pacemaker lateral neurons (LNs) – which then transmit the information to downstream neurons. LNs also modulate the visual system signal in a clock-dependent manner. The electrical properties of LNs are important to the circuit as manipulating their excitability affects the behavioral response. Recently we have found that an additional group of clock neurons (DN<sub>1s</sub>) are also part of this circuit.

We will use the Gal4-UAS system to target expression of different transgenes to either LNs or DN<sub>1s</sub>. Transgenes that alter the molecular clock or neuronal excitability will be used and we will observe the effects on behavior and on internal clocks. We will also use pre- and post-synaptic markers. In this way we will (1) define the function of DN<sub>1s</sub> in the circuit, and (2) determine how information flows between DN<sub>1s</sub> and LNs.

We also aim to develop transcriptional profiles of DN<sub>1s</sub> to complement those recently developed in the lab for LNs. Expressing GFP in DN<sub>1s</sub> will allow their purification by FACS, followed by extraction and amplification of RNA to probe GeneChips. By finding genes specifically expressed in LNs and DN<sub>1s</sub>, we will identify candidate genes that signal between the cells, that can be manipulated to test their role in the circuit.

Understanding how a simple circadian neural circuit operates will help determine general principles by which more complex mammalian circuits synchronize animal behavior and physiology to the environment.

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### **Heather Dean, Ph.D.**

New York University, New York

“Hand-Eye Coordination in Posterior Parietal Cortex”

The coordination of reaches and saccades is behaviorally critical for primates, as we look to accurately reach for or grasp a tool or food. There is strong behavioral evidence that reaches influence saccade reaction times and saccade velocities, indicating a neural link. However, the neural circuitry underlying this coordinated behavior is poorly understood. This project explores the interactions of brain regions involved in reaches and saccades in order to better understand how these networks coordinate behavior. Two regions in parietal cortex, the lateral intraparietal area (LIP) and the parietal reach region (PRR) have been shown to be involved in saccades and reaches, respectively, and may work together during coordinated movements. Parietal lesions disturb coordination of visually guided reaches and saccades.

This project involves the simultaneous use of up to 8 electrodes in two distinct areas, allowing us to study the interactions of neural circuits rather than responses of single units alone. Recording the local field potential (LFP) in addition to cell spiking will enable us to more closely examine interactions between areas specialized for reaches and saccades. A number of studies have reported correlations

between spike and LFP recordings in the same cortical area but none have analyzed spike-field correlations across multiple areas. Correlations in the LFPs or between spiking activity in one area and LFPs in another will indicate whether these areas share common inputs or direct connections. We will also directly test for anatomical pathways between circuits in LIP and PRR using microstimulation. We can then correlate the strength of correlation between pairs of sites with the results of microstimulation. This will allow us to determine the extent to which anatomical connections between a pair of sites determines the strength of their functional connections.

These experiments will allow us to better understand the coordination of reaches and saccades and how parietal regions encoding spatial information about these actions interact with one another.

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**Daniel Dombek, Ph.D.**

Princeton University, New Jersey

“Understanding the Neural Mechanisms Responsible for Working Memory”

The cellular and network basis of working memory has yet to be discerned, leaving the mechanisms responsible for tasks such as motor control, spatial navigation and decision making unclear. Neural integration, transient stimuli producing sustained cell or network spiking, is one of the simplest forms of working memory. Recent work has found that synoptically isolated single neurons in the entorhinal cortex, can maintain graded levels of persistent activity, creating broad interest in their possible involvement in the integrating circuits responsible for working memory. The proposed project will investigate multiple hypotheses implicating hysteretic dendritic compartments,  $Ca^{2+}$  wave-fronts and/or discrete  $Ca^{2+}$  thresholds as the source of the single cell graded persistent activity. These hypotheses generate clear predictions that can be tested with various imaging modalities and electrophysiological techniques. Though it is clear that intrinsic neuronal mechanisms can generate graded persistent activity, it is also essential to understand the network interactions for these neurons; no studies to date have focused on their network functions. Through a combination of population imaging and single and dual electrode recordings, these interactions will be studied and possibly linked to system robustness and recently characterized mammalian self-navigation behaviors. Together, these studies will establish the cellular mechanisms, network interactions and possible behavioral involvement of single cell graded persistent activity. The mechanisms learned by studying this system could provide both a specific model for neural integration and a general framework for understanding working memory and its clinical implications in injury and disease throughout the brain.

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**Kevin Franks, Ph.D.**

Columbia University, New York

“Sensory Integration in Olfactory Cortex”

Olfactory information is first encoded in a combinatorial fashion by olfactory bulb (OB) glomeruli, which individually represent distinct chemical features of odors. This information is then transmitted to olfactory cortex (OC), via axons of OB mitral and tufted (M/T) cells, where it may form the odor percept. The circuitry and mechanisms underlying the integration of sensory information in mammalian OC are unclear. We propose two sets of experiments to characterize the transformation of olfactory information from OB to OC. First (Specific Aim1), we wish to determine how many glomeruli

innervate single cells in OC. We will infect OC neurons with a replication-incompetent pseudorabies virus containing a lox-Stop-lox cassette between a CMV promoter and GFP. We will then rescue replication and express Cre recombinase to induce GFP expression by in vivo patch-clamp dialysis of single OC neurons. GFP-expressing virus will only infect M/T cells that make synapses onto the patched OC cell and, by labeling these M/T cell dendrites, identify the subset of glomeruli innervating the patched OC cell. These experiments will determine how many classes of inputs single neurons in OC receive. To complement this anatomical study, we will also functionally characterize the transformation of sensory information from OB to OC (Specific Aim 2). We will generate a transgenic mouse line in which M/T cells express the light-activated cation channel, Channelrhodopsin 2. To determine the number of glomeruli functionally innervating single OC cells, we will make in vivo patch-clamp recordings in OC while photoactivating individual dorsal glomeruli. To determine whether multiple cells from one glomerulus innervate a single cell in OC we will compare the amplitudes of synaptic responses evoked by stimulating single M/T axons and responses evoked by photoactivating a glomerulus. Finally, we will determine how different inputs are integrated by synchronously photoactivating specified combinations of glomeruli. Data generated by these experiments will determine both the minimum number and the possible combinations of glomeruli that can activate an OC cell. These experiments will characterize the transformation of sensory information from OB to OC. Moreover, these experiments will characterize the integration of independently encoded sensory inputs.

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**Adam Hantman, Ph.D.**

Columbia University, New York

“Role of Clarke's Column in Proprioceptive-motor Feedback”

Goal-directed neural computations underlying voluntary movements use sensory information in the construction of motor plans. Sensory systems influence these computations, in part, through feedback control. Feedback control of voluntary movements is carried out by neuronal circuits that compare sensory and motor information to detect discrepancies between actual movements and the intended motor commands. Proprioceptive sensory information, sense of muscle and skeletal position, is well-suited to provide the sensory information necessary for feedback control of voluntary movements. Hindlimb proprioceptive information is fed into feedback control systems by neurons of Clarke's column. Clarke's column receives proprioceptive input from dorsal root ganglia neurons and transforms this raw sensory information into reafference copies. These reafference proprioceptive copies are transmitted to the cerebellum where they are compared to motor efference copies and corrective motor commands are generated. To begin to investigate the role of reafference copies generated in Clarke's column, we will use mouse genetics to inactivate all or classes of Clarke's column neurons. Genetic inactivation of Clarke's column neurons requires the identification of genes selectively expressed in this nucleus. We will use a candidate screen approach and an unbiased gene array approach to identify such genes. Thus far, the candidate screen approach has yielded two selective markers of subsets of Clarke's column neurons. We will develop behavioral tests to assess the voluntary motor deficits resulting from the inactivation of Clarke's column neurons. Phenotypes resulting from the inactivation of subsets of Clarke's column neurons will be best understood if the character of the reafference copies generated in each of these classes is known. The character of reafference copies will be described by exploring the input-output relationships of the genetically defined classes of neurons. If successful, this will be the first selective loss of function study of Clarke's

column and should provide insight on how sensory information is used in goal-directed neural decisions.

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**Susana Lima, Ph.D.**

Cold Spring Harbor Laboratory, New York

“Neural Mechanisms Underlying Selective Attention in the Rodent Auditory Cortex”

In our daily life we are continuously bombarded by an enormous amount of sensory information, most of which is irrelevant to the process of executing our goals. This poses a serious challenge for our brain, since we have limited resources to process information. To solve this problem, we must select from the entire available information the relevant and necessary subset to execute our actions, while ignoring the rest. One mechanism used by our brain to achieve this goal is attention, a cognitive operation by which the brain filters out the relevant information, and directs resources to the important aspects of what we experience.

I am interested in understanding the neural mechanisms and circuits underlying selective attention. Specifically, I propose to characterize the modulation of neural activity by selective attention, using the rat auditory cortex as model system. My hypothesis is that the subpopulation of neurons in the auditory cortex that project to higher brain structures known to be involved in spatial attention will be preferentially modulated during a selective attention task.

My specific aims are:

1. Probe the neural correlates of an auditory selective attention task in the auditory cortex of freely moving rats using extracellular recordings. In this task, animals will be required to pay attention to either the spatial or frequency properties of the same acoustic stimulus in order to be rewarded.
2. Examine whether different populations of neurons are differentially modulated by attention during this task. For this aim I will develop a new technique for distinguishing populations recorded in vivo during behavior, based on the pathway-specific expression of the light-activated protein ChannelRhodopsin-2.

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**Shin Nagayama, Ph.D.**

Yale University, Connecticut

“Individual Neuronal Contributions to the Functions of a Cortical Network Module”

What is the neural basis of perception? To understand this question, we first need to understand brain function at the neuronal network level. One attractive model of brain function has been based on multi-neuronal anatomical and functional units such as a cortical column, barrel or glomerulus. Despite much study, the neural basis of the function of these functional units has remained unclear because it is difficult to detect individual neuronal activities in the context of their neuronal networks. The goal of this research project is to investigate how information is processed within the glomerular module, the multi-neuronal network unit in the olfactory bulb. This will in turn, allow us to understand the basic function the glomerular unit plays in odor coding and smell perception.

Over the past two years, I have developed a new technique to visualize a neuronal network and its activity by electroporation of dextran conjugated  $Ca^{2+}$  sensors into a local neuronal circuit. Using this technique, we have succeeded in visualizing multi-neuronal structures in the context of their neuronal

circuits with subcellular resolution, as well as detect  $\text{Ca}^{2+}$  responses in the compartments of the labeled neurons. We now plan to apply this technique to the functional analysis of the neuronal network units in the olfactory bulb. The basic question is: do the projection neurons associated with the same glomerular module respond to the odorant stimulation in a similar way? We plan to address this question anatomically and functionally using our newly developed neuronal labeling technique with in vivo two-photon microscopy.

Overall this project aims at addressing the fundamental neural basis of psychological experience. Based upon the results, future projects will investigate the individual neuronal interactions that occur between glomerular units with the aim of gaining a more comprehensive understanding of the function of larger scale neuronal networks.

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### **Anne-Marie Oswald, Ph.D.**

New York University, New York

“Functional Sub-circuits in Primary Auditory Cortex”

A central issue in auditory neuroscience is how the acoustic environment is represented by neural activity in the primary auditory cortex (AI). The firing properties of AI neurons are influenced by both thalamic input and the local network of pyramidal cells and interneurons. The long term objective of this proposal is to investigate how the combination of cortical circuitry and synaptic dynamics in AI in shapes the neural responses to acoustic stimuli.

Interneurons are postulated to sharpen neural tuning in AI through lateral inhibition. However, the circuitry underlying this phenomenon has yet to be fully characterized. The experiments described in this proposal investigate interneuron-PC interactions using simultaneous whole cell recordings of neurons in a thalamocortical slice preparation of AI. Preliminary studies show a high probability of reciprocal connection between pyramidal cells (PCs) and fast-spiking (FS) interneurons in L2/3. Moreover, high frequency stimulation of an FS cell produces significantly stronger inhibition in non-reciprocally connected PCs than in reciprocally connected PCs.

These results suggest that there are sub-circuits that consist of FS cells and their reciprocally connected PCs. These circuits competitively interact through non-reciprocal inhibitory synapses. This combination of circuit architecture and synaptic dynamics may, in effect, produce lateral inhibition between FS-PC sub-circuits that reduces the neural response to non-preferred stimuli.

Specific Aims:

Aim 1: Reciprocally connected FS-PC pairs form distinct sub-circuits. These studies characterize the scope of reciprocally connected (RC) FS-PC sub-circuits, the extent of their interactions with other sub-circuits through non-reciprocal inhibitory connections, and their inputs from layer 4.

Aim 2: Differential synaptic responses between RC and non-RC FS-PC pairs. These experiments will determine if the increased inhibitory input to non-RC pyramidal cells is due to the increased activation of  $\text{GABA}_B$  receptors at these synapses.

Aim 3: The functional contribution of FS-PC sub-circuits to the processing of acoustic input. A model network will be developed that incorporates the experimentally determined patterns of reciprocal and non-reciprocal FS-PC connections and their differential inhibitory synaptic responses. This model will

be used to test the hypothesis that non reciprocal inhibitory connections between FS-PC sub-circuits reduce neural responses to non-preferred stimuli through lateral inhibition.

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**Eva Pastalkova, Ph.D.**

Rutgers University, New Jersey

“Internally Generated Assembly Sequences in the Hippocampus and Episodic Memory”

Conclusions about the function of a brain structure often depend on the observational methods used. Single unit studies in rodents indicate that the hippocampus and associated structures are involved in spatial navigation, whereas studies in humans have provided firm evidence that hippocampal networks are critical in coding and retrieval of episodic memories. It has been repeatedly hypothesized that networks that serve spatial navigation may be ideal to represent episodes. A necessary condition for supporting this idea would be the demonstration that hippocampal networks can advance their intrinsic activity in the absence of external control cues, mimicking internally controlled free recall in humans. I provide preliminary evidence here showing that cell assembly sequences in the hippocampus evolve perpetually even where rats are ‘frozen’ in space (i.e., running in a wheel) and suggest the merit of exploring the hypothesis that hippocampal cell assemblies can be generated by the internal dynamics of the network. Specifically, I propose to investigate (a) whether the different environmental contexts will give rise to unique evolving population sequences while the rat runs in the same wheel, (b) whether we can identify the conditions that initiate those sequences, (c) how cell assembly sequences are affected by transient (2 sec) inactivation of all neurons in the hippocampus and (d) whether we can predict the future choice of the rat in the delayed spatial alternation task from the perpetually shifting sequence episodes during wheel running (i.e. the delay time). These physiological findings will provide a link to understanding the mechanisms of episodic free recall. Hopefully, they will also provide an alternative coding mechanism of working memory, distinct from persistent activity of a circumscribed cell assembly.

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**Kira Poskanzer, Ph.D.**

Columbia University, New York

“A Two-photon Blueprint of the Neocortical Microcircuit”

The long-term goal of this project is to understand the computational logic of the cortex at the circuit level. To accomplish this, I propose to re-construct microcircuits of linked cortical neurons in mouse primary sensory cortex using a novel optical technique. New techniques are necessary because, so far, it has been difficult to identify and characterize more than two closely-spaced, connected cells in the cortex. Thus, to understand how myriads of cells (and cell types) form a microcircuit, we need methods that reveal large numbers of connected cells. In order to detect chains of connected cells, I will use two-photon laser uncaging of glutamate to sequentially activate neurons in neocortical brain slices in a large-scale, unbiased, and proximity-independent manner. I will start with a particular class of layer 5 pyramidal neuron, and use this technique to find potential presynaptic inputs. Carried out repeatedly, I will identify polysynaptic strings of connected neurons, which will be characterized electrophysiologically and morphologically. Using this data, I will assemble the first "blueprint" of a cortical microcircuit, and by performing similar experiments in two different cortical areas, establish the commonality of circuits used for different modalities. Finally, to investigate circuit plasticity, I will

describe the circuit connectivity over time, and probe its molecular determinants using pharmacology and electrophysiology.

The characterization of functional cortical microcircuits will be relevant to fundamental questions in brain circuitry. First, it will help to determine whether synaptic connections between cells develop in a specific or a probabilistic, or even random, manner. Second, comparing microcircuit diagrams across cortical regions will clarify whether a canonical microcircuit may exist and, by extension, how generalized information processing may be throughout the cortex. Third, it will be possible to use the circuit diagram to ascertain whether connectivity dynamics may underlie nervous system changes and be a novel form of neural plasticity. Finally, the outcome of these experiments—both connectivity and plasticity—will inform and broaden the results of the other and could have significant implications to studies of both the developmental control of circuit formation and computational modeling of the cortical circuit.

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**Jonathan Touryan, Ph.D.**

Yale University School of Medicine, Connecticut

“Neural Basis of Feature Attention in Area V4”

Visual attention plays a key role in determining which information is actively processed by the visual system. Without attentional guidance, the visual system would be overwhelmed with stimuli – stimuli that are mostly irrelevant for any given behavioral task. Over the last several decades the neural substrates of visual attention have been explored, with most studies focusing on the spatial aspects of visual attention (i.e., directing attention towards specific locations in space). These experiments show that spatial attention significantly modulates the responses of visual neurons in extrastriate cortical areas like V4 and MT. In contrast, feature attention has been less studied. During natural behavior, feature attention is likely involved every time an individual depends on a specific visual feature or set of features to distinguish a target object from a cluttered background. While the effects of feature attention have been well quantified in human psychophysics, their neural basis is far less well understood.

Here we propose a method to quantify the effects of feature attention on the selectivity profiles of neurons in area V4. Specifically, we will address whether feature attention can modify visual selectivity profiles of V4 neurons in a manner analogous to how spatial attention alters receptive field properties in V4. We will approach this question by first quantifying the selectivity of V4 neurons to visual features in natural scenes. Using a method adapted from psychophysics, we will localize the features in complex natural images that elicit spiking activity. To quantify the effects of feature attention, we will use a standard visual search paradigm to analyze the changes in visual selectivity as a function of the search target. This analysis will indicate the degree to which V4 neurons change their selectivity profile to match the visual properties of the search target.

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**Chun-I Yeh, Ph.D.**

New York University, New York

“Spatio-temporal Receptive Fields of Single Neurons in Different Layers of Macaque V1”

The primary visual cortex (V1) is the first cortical stage of visual perception. Visual information encoded in the retina enters the input layer 4 of V1 through the visual thalamus and in turn is sent to layers 2/3 that project to extrastriate cortex. Understanding V1 circuitry offers invaluable insight about the general rules of cortical organization. One approach to study V1 functional organization is to investigate how the spatio-temporal receptive fields of single neurons evolve from the input to the output layers of V1. Several receptive-field mapping techniques applying reverse correlation analysis (e.g. sparse noise and checkerboard-like white noise) have been successful in capturing spatial and temporal properties of neurons in the early stages of visual processing (Jones & Palmer, 1987; DeAngelis et al., 1993; Reid et al., 1997). These methods, however, seem to be less effective in mapping neurons in the output layers of V1 (e.g. Martinez et al., 2005). Interestingly, recent studies from our group have found that many neurons in both input and output layers of macaque V1 are mappable with the subspace reverse correlation technique developed by Ringach et al (1997). This dynamical mapping technique allows us to compare directly the receptive fields of neurons at different processing stages of V1. In this research project, we propose to study the spatio-temporal receptive fields of cortical cells in different layers of macaque V1 by using a multi-electrode matrix. This matrix consists of seven independently moveable electrodes, which allow us to record simultaneously from multiple neurons at nearby visual eccentricities (within the same layer or in different layers) and to collect data from a large cell population in each V1 layer. We also will measure receptive fields of V1 neurons with other mapping techniques (with sparse noise, the checkerboard-like white noise, as well as the subspace reverse correlation technique). Overall, the results of these studies are crucial for the understanding of V1 circuitry and for the development of multi-layer computational models of V1 cortex.

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**Manuel Zimmer, Ph.D.**

The Rockefeller University, New York

“Reprogramming of Neural Circuits in *C. elegans* to Regulate Feeding States and Social Behavior”

Various behaviors can be encoded by one neural circuit. This multiple coding is achieved by neuromodulatory regulation of circuitry. For example, behavior is biased by internal states, such as hunger, satiety, arousal, anxiety, aggression or social attachment. Chronic failure in neuromodulatory homeostasis is associated with mental diseases like depression or anxiety disorders. The objective of my postdoctoral work is to use *C. elegans* as a model system to investigate how neural circuits systemically change in different internal states and to ask for the underlying molecular mechanisms.

Due to its simplicity, the nervous system of *C. elegans* is ideal to study neural circuits. Only 302 neurons interconnect in a stereotypic fashion. Nevertheless, *C. elegans* generates sophisticated behaviors like chemotaxis and social feeding. I am investigating two interrelated behaviors: oxygen chemotaxis and social feeding. A student and I have developed a simple behavioral paradigm to assign quantitative behavioral values to the activity of individual neurons. Strains that exhibit different social behaviors and animals under different feeding states respond qualitatively differently in this assay, suggesting a key role for neuromodulatory mechanisms.

The aim of my studies is to map the underlying neural circuit by identification of critical sensory- and interneurons by ablation methods. Circuit mapping will be performed under different conditions, comparing solitary versus social animals, and animals in different feeding states. This analysis will reveal

the critical components that change to alter behavior. I recently developed Ca<sup>2+</sup>-imaging technologies to measure activity of neurons in animals that experience changes in environmental oxygen levels. I will apply this technology to examine the physiological changes in the critical cells. I will perform genetic studies of a neuropeptide, FLP-8, to reveal the underlying mechanisms of neuromodulation.

My studies aim to provide new information about how neural circuits are dynamically organized by behavioral states, both from a systems viewpoint and on the cellular and molecular level. Such comprehensive research is currently difficult in higher vertebrates but the basic machinery of neuromodulation is conserved between species. Therefore, I believe my work will reveal principles that are relevant in higher animals including humans.