The Division of Neurobiology and Behavior

Michael Goldberg, MD, Division Chief
Department of Psychiatry, Columbia University
College of Physicians and Surgeons
New York State Psychiatric Institute
April 1, 2012 - March 31, 2013

Overview

The Division of Neurobiology and Behavior consists of seventeen independent basic research laboratories in the Kolb Research Annex. The research philosophy shared by the division's faculty holds that an integrated approach, ranging from cellular and molecular biology to neural systems and behavioral analysis, is required to understand the basis of normal and abnormal human behavior. As part of this endeavor, experimental approaches are complemented by a broad range of theoretical and computational techniques.

The main foci of research in the division are on basic science aspects of neural development and on the functions of the nervous system that underlie normal and abnormal behavior. The subjects investigated in these studies range from simple invertebrates to humans. Many of the studies carried out in the division focus on processes such as learning and memory, attention, perception, and affective behavioral traits that may be involved in mental illness. Several ongoing projects may someday contribute to the field's understanding of the etiology of, and new therapeutic approaches to, anxiety disorders, benign-age-related memory loss, cerebral palsy, fragile-X syndrome, Rubinstein-Taybi Syndrome, schizophrenia, and spinal cord trauma.

Current Research

Craig Bailey: My laboratory has continued to examine the cellular and molecular mechanisms that underlie the synaptic remodeling and growth that is induced by learning. Toward that end, we have extensively studied the storage of long-term memory for sensitization of the gill-withdrawal reflex in *Aplysia* and have found that it is associated with the growth of new synapses by the sensory neurons onto their postsynaptic target neurons. Despite the association of synaptic growth with various forms of long-term memory, surprisingly little is known about the cell biological mechanisms that regulate and couple the structural changes to the molecular changes that govern learning-induced synaptic plasticity and the relative functional contribution each may make to the initiation of the long-term process on the one hand and its stable maintenance on the other. To address these questions, we have collaborated with Eric Kandel and have combined time-lapse imaging and molecular biological analysis (using gene transfer) of living sensory-to-motor neuron synapses in culture and have monitored both functional and structural changes simultaneously so as to follow remodeling and growth at the same specific synaptic connections continuously over time. This approach has allowed us to examine directly the functional contribution of learning-related

structural changes to the different time-dependent phases of memory storage. Insights provided by these studies suggest the synaptic differentiation and growth induced by learning in the mature nervous system are highly dynamic and often rapid processes that can recruit both molecules and regulatory mechanisms important for *de novo* synapse formation during development.

Mark Churchland: Professor Churchland studies how the brain generates voluntary movement. The ease with which we direct our bodies is truly remarkable. Only when faced with dis-function do we ponder that voluntary movement is not to be taken for granted. It is the product of sophisticated neural machinery that allows us to easily outperform the most sophisticated of robots. But what is the nature of this neural machinery? How does it function in wellness? How does it malfunction in disease, and how might we fix it? To answer such questions, Dr. Churchland studies the performance of difficult movements while simultaneously recording from large neural populations. http://churchlandlab.neuroscience.columbia.edu

Aniruddha Das: My lab uses alert, task-engaged animal models – primarily macaque monkeys and more recently, mice – to study the neural basis of the brain imaging signal. Our results are of direct relevance to the interpretation of fMRI in humans. **Research:** Earlier (Sirotin and Das, *Nature* 2009) we had shown that the brain imaging signal recorded from primary visual cortex (V1) of alert monkeys contains a prominent signal component - labeled **'task-related signal'** - that is independent of stimulus input or local spiking. When the animals perform periodic tasks this signal entrains to the task timing, bringing a peak of local arterial blood volume to V1 in time for predicted trial onsets.

The presence of this large task-related signal, unrelated to local spiking or LFP, complicates the interpretation of fMRI signals in terms of local neural activity. One part of the effort in my lab is thus directed to understanding the implications of this signal for neuroimaging. Recently we showed that when subjects are engaged in a stereotyped task, the task-related signal can be subtracted away linearly leaving a stimulus-evoked signal that is strikingly well predicted by local neural spiking (> 93% of the variance explained; as vs. ~ 50% when the task-related signal is not subtracted (Cardoso et al., *Nat. Neurosci* 2012)). However, not subtracting the task-related signal can severely distort estimates of local neural activity deduced from the imaging signal. This finding has obvious implications for the proper task design for imaging studies. Notably, we also see that spiking is a far better predictor of stimulus-evoked hemodynamics than is gamma-band LFP. This finding is contrary to the dominant belief in the field, and it questions the underlying idea that the hemodynamic signal reflects metabolic demand and thus synaptic processing (Logothetis et al., *Nature 2001*). Results from this work will thus likely continue to be of great significance to the understanding of functional brain imaging.

In a complementary approach, we are studying the behavioral and neural correlates of the task-related signal. We hypothesize that it reflects a novel mechanism of arousal or attention that affects hemodynamics independent of local spiking. For example, this signal increases sharply with increasing reward size. When the task timing is variable, this signal increases with increasing stimulus anticipation. Further, the stimulus is closely tied with task performance: the signal amplitude is sharply reduced on incorrect trials; and the size of the signal when the animal is waiting for a trial to start can predict the likelihood of the animal giving the correct answer. We are therefore systematically exploring these behavioral correlates of the signal in alert, task-engaged macaques. At the same time, we believe the signal is evolutionarily conserved across species. In collaboration with Randy Bruno we have preliminary data showing the presence of a similar signal in barrel cortex of mice trained to perform periodic detection tasks with their whiskers. We plan to use the mouse model to explore, aggressively, the neural basis for this task-related signal.

Michael E. Goldberg: My lab investigates the physiology of cognitive processes such as spatial perception, attention, arousal, and decision-making, studying the activity of single neurons or multiple single neurons in monkeys trained to do difficult visual and oculomotor tasks. **Research:** We are studying the role of somatosensory cortex in spatial perception. Some years ago we discovered that there is a representation of eye position in area 3a of the monkey somatosensory cortex. We have now discovered that cooling somatosensory cortex removes eye position effects in monkey parietal cortex, but does not affect the monkey's performance on a spatially demanding task that is affected by parietal lesions in humans.

Most studies of neural function in the monkey concentrate on sensorimotor activity, for example track activity from the retina to the eye muscles when a monkey makes a visually guided eye movement. We have discovered that the baseline activity of parietal cortical neurons, which occurs when an animal is waiting for a task to begin but does not have any sensorimotor plan, predicts how well the monkey will perform on the current trial, and reflects his history of success or failure on past tasks. The actiivty is not related to the monkey's locus of visual attention, or to any spatial aspect of the task. Iontophoretic application of nanomole amounts of acetycholilne onto single neurons while the monkey is performing a difficult visual search task increases both the sensorimotor and the baseline activity of parietal neurons. Nicotinic and muscarinic antagonists decrease both baseline and sensorimotor activity.

Recording the activity of two neurons simultaneously, neither or which can be driven from a stimulus in the other neuron's receptive field, we have discovered that during the baseline period noise correlation between the neurons is high, suggesting that the activity is driven by a non-spatial, reward-related signal. The sensorimotor aspect of the task drives down the noise correlation. In collaboration with Ken Miller we are using a network model to explain this

activity. The increase in noise correlation in the baseline period is further evidence for the importance of nonspatial modulatory signals in the control of behavior.

Jacqueline Gottlieb: Our laboratory investigates the neural mechanisms of decision making with a particular interest in working memory and attention. We investigate these functions using behavioral testing in humans and monkeys and neurophysiological recordings in monkeys, and are particularly interested in the parietal and frontal lobes.
Research: We recently discovered a large areal difference, whereby the inhibition of distracting information is much stronger in the frontal than in the parietal lobe, suggesting that the two areas have circuitry and functions that are more distinct than had been previously appreciated. We have also recently discovered that the parietal cortex reflects the correlates of attentional orienting based on novelty and reward associations; these forms of orienting are distinct from other types of attention because they depend on learnt stimulus properties (rather than simply on stimulus contrast) but nevertheless act automatically and can be distracting in an ongoing task. Finally, in collaboration with a developmental robotics group, we are pursuing behavioral and computational studies examining the mechanisms of curiosity and intrinsic motivation in human observers.

Bob Hawkins: Overview: My lab is continuing to investigate cellular mechanisms of learning and memory in *Aplysia* and hippocampus. Recently, these studies have focused on the role of spontaneous transmitter release in learning-related synaptic plasticity. Research: My lab has found that spontaneous transmitter release plays an unexpected and important role in learning-related synaptic plasticity in *Aplysia*. As in other preparations, learning and plasticity in *Aplysia* have an early phase that involves covalent modifications that are restricted to one side (in this case presynaptic) of the synapse, and a late phase that involves growth and remodeling of synapses and thus requires changes on both sides. How is plasticity transferred from one side of the synapse to both, and when does that occur? We have found that enhanced spontaneous transmitter release from the presynaptic neuron during the early phase acts as an anterograde messenger to recruit postsynaptic mechanisms of intermediate-term plasticity, which are in turn early steps in a synaptic growth cascade leading to long-term plasticity. We are continuing to investigate other steps in that cascade, and to explore the possible roles of spontaneous transmitter release in other types of plasticity and species.

Eric Kandel: The Kandel lab explores the molecular mechanisms of memory storage in both the sea slug *Aplysia* and in mice, as well as animal models of memory disorders, mental illness, and drug abuse.

Recently, the Kandel lab followed up on their studies of the role of small regulatory RNAs in the timing of learning-related synaptic plasticity. A parallel

sequencing screen in *Aplysia* revealed that in addition to microRNAs, a population of Piwi-interacting RNAs (piRNAs) were found in the brain. The finding of piRNAs in the brain was surprising, as they were previously thought to be restricted to germ cells. As is the case with germ cells, the piRNAs in brain do not have a double-stranded precursor and are associated with Piwi protein. The piRNAs in the Aplysia CNS have a predominant nuclear localization and a robust increase in expression in response to serotonin, a modulatory transmitter important for memory. They found that the Piwi/piRNA complex facilitates serotonin-dependent methylation of a conserved CpG island in the promoter of CREB-2, the major inhibitory constraint of memory in *Aplysia*, leading to enhanced long-term synaptic facilitation. The finding of a piRNA whose inhibition of CREB-2 is upregulated by serotonin and the earlier finding of microRNA22 that inhibits CREB-1, the activator of long-term memory that is down-regulated by serotonin, provide a small RNA-mediated gene regulatory mechanism acting on both the nucleus and on cytoplasmic mRNAs to establish stable long-term changes in the sensory neurons for the persistence of memory (Rajasethupathy et al. 2012).

Ning Qian: We are interested in computational modeling of neural systems, particularly visual and motor-control systems. We also conduct psychophysical studies of face perception and psychiatric disorders. In a recent study cited above, we applied an infinite-horizon stochastic optimal feedback control model to explain movement duration, as well as movement trajectory, of reaching movements. We were able to derive analytically both the log and power forms of the Fitts law.

Daniel Salzman: The Salzman lab investigates neural mechanisms that mediate cognitive and emotional processes.

Traditionally, scientists have conceptualized particular brain areas as performing emotional functions, and others as implementing cognitive ones. Today, scientists often contend that the amygdala implements emotional behavior, while prefrontal cortex (PFC) mediates cognitive operations. Work in my laboratory has challenged this traditional view by emphasizing how the representation of emotional and cognitive parameters are intertwined in the amygdala and PFC, and how the amygdala participates in both appetitive and aversive emotional processes. Conceptualizing the amygdala as purely an emotional structure hampers our ability to understand the manner in which cognitive and emotional functions are inextricably linked in the amygdala. Recent and ongoing studies in my lab suggest that the amygdala sits at the nexus of emotion-cognition interactions. We demonstrate this by utilizing tasks in which cognitive and emotional processes interact, and then study neurophysiological processes mediating these interactions. In recent work, we seek to manipulate input to the amygdala that normally must carry cognitive information to understand how it alters the processing of emotional information by single amygdala neurons.

Sam Schacher: We are examining the cellular and molecular bases of activity-dependent persistent synaptic plasticity and its reversal by inactivity or other forms of circuit activity. These changes at synapses are the cellular correlates of learning and memory on the one hand and forgetting on the other. Mature neural circuits, especially their synaptic connections, can be modified by activity/experience that is generally believed to encode leaning and memory. Since some memories are persistent, while others are forgotten, specific cellular and molecular processes evoked by the initial experience and subsequent activity regulate the amplitude and duration of changes in a key feature of neural circuits – strength of synaptic connections. We have found that interactions of cell adhesion molecules, activation of sequential cascades of specific signaling pathways involving the timely secretion of neurotrophin-like peptides with autocrine and paracrine actions, and the timely cell-specific activation of bZIP transcription factors CREB1, CREB2 and cJun contribute to persistent long-term plasticity and its reversals. We wish to understand how the timely activations of these pathways produce specific regulation of gene transcription/activation, local and cell-wide protein translation, and the network of interacting processes that regulate the maintenance and strengths of synapses in a mature neural circuit. These studies will provide important insights into how neural circuits modified by experience either revert back to baseline ('forget') or maintain new levels of synaptic strength induced by the experience ('remember').

Steve Siegelbaum: The Siegelbaum laboratory examines how the electrical properties of neurons regulate information flow through the hippocampal circuit during memory storage. Studies focus on the importance of a specific type of ion channel located in hippocampal neuron dendrites for controlling long-term plastic changes in synaptic transmission that are thought to contribute to learning and memory.

Research: Over the past year our laboratory has elucidated the mechanism by which the HCN1 ion channel is specifically targeted to the distal dendrites of hippocampal CA1 pyramidal neurons, where it acts as an inhibitory constraint of both hippocampal synaptic plasticity and spatial learning and memory. We find that the extracellular matrix glycoprotein reelin is critical for the proper targeting of the channel to its dendritic locale. This effect requires intracellular signaling through DAB1 and the tyrosine kinase pathway. Disruption of HCN1 targeting may contribute to altered brain function in various neurological and psychiatric disorders that are thought to interfere with reelin signaling.

Eleanor Simpson: This work is aimed at dissecting components of the negative symptoms of schizophrenia, particularly the deficits in incentive motivation. These symptoms represent major barriers to patient's functional outcome and quality of life. By studying the neurobiology of the specific aspects of motivated behavior that are disrupted in patients with schizophrenia we hope to better understand the etiology of the symptoms and find potential treatment targets.

This work is conducted in collaboration with Eric Kandel (Neurobiology and Behavior) and Peter Balsam (Cognitive Neuroscience).

Education and Training

Professor **Churchland** gives lectures in graduate and upper-level undergraduate courses. **Gottlieb:** We have mentored many postdoctoral associates, as well as graduate and undergraduate students and even high school students. **Siegelbaum:** I participate in the teaching of medical and graduate students through lectures, small group discussions and supervision of Ph.D. thesis research. **Bailey:** I currently co-mentor 3 students in Eric Kandel's lab. **Schacher:** I am a co-director (along with Craig Bailey) of the neural science course taught to second year medical and dental students at P & S. Besides the administrative aspects of the course, I will present several lectures and lead a small group discussion on human neuroanatomy. **Hawkins:** I continue to teach in courses on "Synaptic Transmission" and "Survey of Neuroscience" for graduate students, and "Basic and Clinical Neurosience" for medical students. **Das:** 1 former graduate student (and later, postdoc) who now has an independent position: Yevgeniy B. Sirotin, currently an independent research fellow, Rockefeller University.

1 new postdoctoral research fellow (Bruss Lima, starting Oct 2010).1 continuing graduate student (Mariana Cardoso) **Qian:** I participate in teaching the Neural Science course at Columbia University Medical Center. **Salzman:** I am the training director of an NIMH sponsored training grant (T32) which trains psychiatrists and other postdoctoral fellows to become independent investigators. I also supervise postdoctoral fellows and graduate students in my lab. Finally, I teach medical and dental students. **Goldberg:** I have had one neuroscience graduate student in my lab. I teach clinical neurology on the Consult Hospitalist Division at NYPH, a rotation which always has a PGY 1 Psychiatry Resident, and give a number of neuroscience sections to medical students in the neuroscience course. I have postdocotral fellows, one of whom, Linus Sun, just won a K08 clinician-scientist mentored research award.

Honors and Awards

Bailey: Simons Foundation Autism Research Initiative Investigator Award. Neurexin-Neuroligin Trans-Synaptic Interaction in Learning and Memory. Co-PI (07/01/2008 – 06/30/2013). To study the role of the neurexin-neuroligin interaction in learning-related plasticity in order to gain insights into the dysfunction of synaptic remodeling, maturation, and stabilization that may represent important, contributing cellular underpinnings of autism- spectrum disorder (ASD).

Churchland: is a recipient of the 2012 NIH Directors' New Innovator Award. He received a 2013 McKnight Scholar Award, a 2013 Sloan Research Fellowship,

and a 2012 Search Scholars Award. He was a 2006 recipient of the Burroughs Wellcome Fund Career Award and a 2003 recipient of the Helen Hay Whitney Research Fellowship.

Das: Grant "Task-related brain imaging signals in alert mice, in parallel with alert monkeys" from the Kavli Institute for Brain Science, Columbia University:
Goldberg: Mentor on the K08 Clinician-Scientist award to Linus Sun.

Gottlieb: National Institute of Mental Health R01 MH-098039-01 2012 Attentional control by uncertainty and reward

Hawkins: I was recently awarded a 5 year R01 from the NIH to study the roles of neurotrophins and their interactions with spontaneous transmitter release in synaptic growth cascades in Aplysia.
Kandel: Eric Kandel was awarded the Child Mind Institute Distinguished Scientist Award, the Adolf Meyer Award from the American Psychiatric Association, and Honorary Doctorates from the University of Basel as well as the Institute for Doctoral Studies in the Visual Arts (Portland, Maine).
Qian: We received an Explorer grant from Simons Foundation to conduct a pilot study on autism.

Siegelbaum: Elected member of the American Academy of Arts and Sciences, Elected member of the Institute of Medicine. R01NS36658, Regulation of HCN channel trafficking and function in the brain by TRIP8b. P.I. S.A. Siegelbaum

Simpson: Postdoctoral Fellow Ina Filla awarded a 2 year stipend from the DAAD (German Academic Exchange Service) to measure extracellular dopamine in a transgenic model of motivational deficit.
Postdoctoral Fellow Estefania Bello awarded a Pew Latin American Fellowship for Biomedical Research to study dopamine release patterns during learning in mouse models of the cognitive deficits of schizophrenia

Publications (Selected)

1. Suzuki M, **Gottlieb J.** Distinct neural mechanisms of distractor suppression in the frontal and parietal lobe. Nat Neurosci. 2013 Jan;16(1):98-104.

2. Rajasethupathy P, Antonov I, Sheridan R, Frey S, Sander C, Tuschl T, Kandel ER. 2012. A Role for Neuronal piRNAs in the Epigenetic Control of Memory-Related Synaptic Plasticity. Cell 149: 693-707.

3. Xu, B., C. Karachi, et al. (2012). "The postsaccadic unreliability of gain fields renders it unlikely that the motor system can use them to calculate target position in space." Neuron **76**(6): 1201-1209. PMID- 23259954

4. M. M. B. Cardoso, Y. B. Sirotin, B. Lima, E. Glushenkova & **A. Das**: The Neuroimaging Signal is a Linear Sum of Neurally Distinct Stimulus- and Task-Related Components. *Nat. Neurosci.* **15(9):** 1298-1306 (pdf)

5. Peck, CJ, Lau, B and Salzman CD. The primate amygdala combines information about space and value. Nature Neuroscience 2013 Mar;16(3):340-8

Divisional Highlights

Das discovered that the cortical hemodynamic signal in the monkey is the linear sum of two signals, one driven by neural spiking and local field potential activity and the other driven by a predictive signal unrelated to actual recordable neural activity.

Goldberg found that eye position modulation of visual responses in parietal cortex lags the actual eye position by at least 150 ms, and cannot possibly used as a mechanism to determine target location for action, a popularly held computational theory.

Gottlieb discovered that the parietal cortex reflects the correlates of attentional orienting based on novelty and reward associations; these forms of orienting are distinct from other types of attention because they depend on learnt stimulus properties (rather than simply on stimulus contrast) but nevertheless act automatically and can be distracting in an ongoing task.

Kandel discovered that piwiRNA, previously thought only to be in germ cells, forms a complex that facilitates serotonin-dependent methylation of a conserved CpG island in the promoter of CREB-2, the major inhibitory constraint of memory in *Aplysia*, leading to enhanced long-term synaptic facilitation.

Salzman found that althogh the conventional wisdom is that the amygdala implements emotional behavior, while the prefrontal cortex (PFC) mediates cognitive operations, emotional and cognitive parameters are intertwined in the amygdala and PFC, and that the amygdala participates in both appetitive and aversive emotional processes.

Schacher found that interactions of cell adhesion molecules, activation of sequential cascades of specific signaling pathways involving the timely secretion of neurotrophin-like peptides with autocrine and paracrine actions, and the timely cell-specific activation of bZIP transcription factors CREB1, CREB2 and cJun contribute to persistent long-term plasticity and its reversals.

Siegelbaum found how the HCN1 ion channel is specifically targeted to the distal dendrites of hippocampal CA1 pyramidal neurons, where it acts as an inhibitory constraint of both hippocampal synaptic plasticity and spatial learning and memory. The extracellular matrix glycoprotein reelin is critical for the proper

targeting of the channel to its dendritic locale. This effect requires intracellular signaling through DAB1 and the tyrosine kinase pathway.