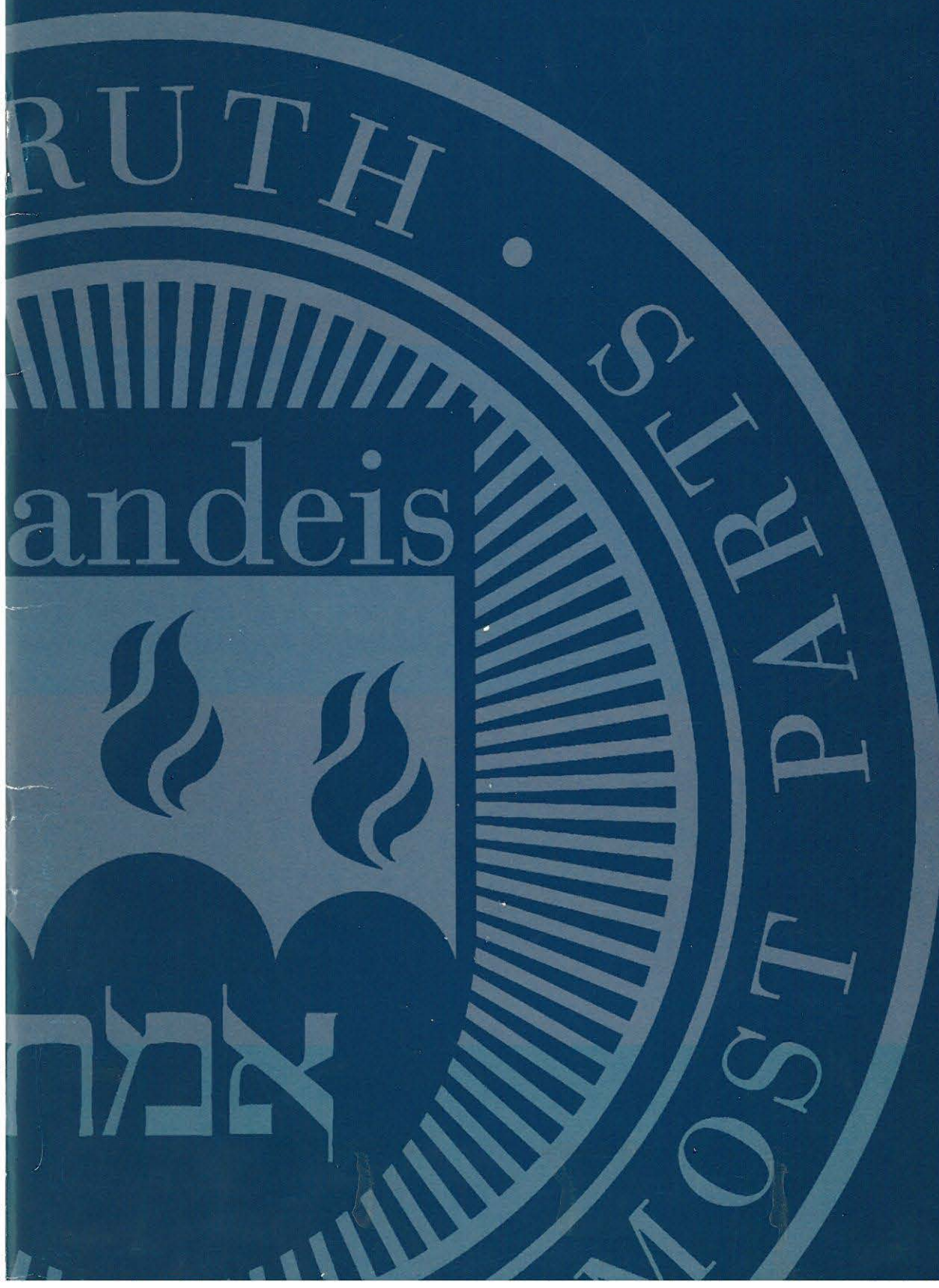

Brandeis University

Benjamin and Mae Volen National
Center for Complex Systems

The M.R. Bauer Foundation
Colloquium Series,
Distinguished Lecturer Series,
and Scientific Retreat

August 2005



The M.R. Bauer Foundation Colloquium Series, Distinguished Lecturer Series, and Scientific Retreat 2004-2005 Summary

Brandeis University

**Benjamin and Mae Volen National
Center for Complex Systems**

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Introduction

The 2005 M.R. Bauer Foundation Colloquium Series, Annual Scientific Retreat, and Distinguished Guest Lecturer Series

It is a pleasure to present this year's proceedings of the M.R. Bauer Foundation Colloquium Series, Annual Scientific Retreat, and Distinguished Guest Lecturer Series at Brandeis University's Volen National Center for Complex Systems. Now in its eleventh year, the generous support of the M.R. Bauer Foundation has enabled my colleagues and me to bring neuroscientists carrying out some of the most interesting work in the field to campus. These proceedings reflect the outstanding lectures that were delivered, but in addition the informal interactions that took place during the speakers' visits also served to enrich the research and educational missions of the Volen Center. At the core of the Volen Center's mission is the mandate to make known the results of its quickly advancing work and to provide a forum for discussing them. I am especially appreciative of the assistance of the M.R. Bauer Foundation, which has facilitated this communication among our faculty and students with so many of the leading practitioners of neuroscience in the United States and throughout the world.

The *M.R. Bauer Colloquium Series* hosted four speakers in 2004-05. These talks focused on vision, stuttering, and taste, and what these systems can tell us about brain function. Dr. **Yang Dan**, an associate professor of neurobiology at the

University of California, Berkeley, spoke about integrating our understanding of plasticity, or adaptability, in the visual system at the synaptic, circuit, and functional levels. How are changes that occur in the synapse, for example, related to simultaneous changes to the visual network? Scientists have studied extensively how visual activities modify the connections between neurons in this system or the overall system itself, but no one has shown how these changes are related. Dr. Dan showed how stimuli can induce changes in the visual system, mediated by the relative timing of electrical inputs and outputs of neurons. The complex patterns of this activity determine the direction and magnitude of changes in the visual system. Dr. **Nancy Kanwisher**, from MIT's Department of Brain and Cognitive Sciences, used functional magnetic resonance imaging (fMRI) of the brain to show how humans recognize the faces of people they know. Dr. Kanwisher is well known for her pioneering work that identified regions of the brain that play specialized roles in the perception of faces, places, and objects. In her recent work, she examined patients with macular degeneration, the central part of whose retinas no longer send visual data to the cortex in the brain for processing. She found the surprising result that the visual cortex was still strongly activated by peripheral stimuli from the retina. This work suggests that large-scale reorganization of the brain and of visual processing takes place in individuals with macular degeneration.

Dr. Kanwisher's findings will likely prove very important for any effort to develop new strategies for rehabilitating patients with this widespread condition.

Dr. **David Rosenfield**, director of the Speech and Language Center at the Baylor College of Medicine, spoke about the neuroscience of stuttering. Using the zebra finch as a model organism for study, Dr. Rosenfield focused on the apparent anomaly that stutterers are fluent when singing. Some one percent of the world's adult population suffers from stuttering. The disrupted speech typical of stutterers is not random but rather likely reflects a disturbance in auditory feedback. An improved understanding of this disruption in speech motor output will contribute to a better general understanding of language processing in the brain. Dr. **Steven Roper**, from the University of Miami School of Medicine's Department of Physiology and Biophysics, looked at signal processing in taste bud cells in order to show that neurotransmitters play a role in cell-to-cell communication. His findings may help to resolve a controversy between scientists who study taste at the molecular level and those who study it at the cellular level. Dr. Roper has demonstrated that taste buds communicate with each other through conventional transmitters such as serotonin prior to signaling the brain.

The 2005 Volen Center Scientific Retreat took place on April 25 at the Charles River Museum of Industry in Waltham, Massachusetts. The event was attended by some 110 faculty, staff, and students, including visitors from other institutions. We were pleased that Jeanette McCarthy, Mayor of Waltham, was there to bring us her greetings. Because of its locale, Dr. **Daniel L. Perlman**, assistant professor of biology at Brandeis, was invited to speak about the New England ecosystem as "another type of complex system worth studying" in a talk entitled "A Brief Ecological History of Boston's Suburbs." He emphasized the diversity of the region in both space and time. Within a hundred miles, there are three regions with very different geological origins. New England has "never been as unchanging and pristine as we once thought." Returning to the meeting's focus on neuroscience, Dr. **Susan Birren**, associate professor of biology and Volen Center, gave a talk entitled "From Heart to Brain: Controlling Neuron Development and Function." It is well known that heartbeat is regulated by the release of a neurotransmitter from neurons embedded in cardiac tissue. Dr. Birren demonstrated that the same neurotransmitter plays a role in regulating the balance between excited and inhibited neurons in the forebrain. Dr. **Jordan Pollack**, associate professor of computer science and Volen Center, spoke about "Recent Progress in Co-evolutionary Learning." Dr. Pollack

has designed robots that use evolution as a means for open-ended self-organization (described during the 2001 Retreat). However, the system works only if fitness is seen as *relative* to other individuals rather than as absolute. Co-evolutionary learning fails when teachers and students become locked into collusive mediocrity—easy questions make both "successful," but the students don't learn anything. With the proper motivational structure built in, based on seeing other players as dimensions of the system rather than as competitors, agents can create continuous progress. Dr. **Daniel Oprian**, the Louis and Bessie Rosenfield Professor of Biochemistry and Volen Center, talked about his work on congenital night blindness in "Mutation of Rhodopsin in Health, Disease, and Sabbatical Leave." Closing fifteen years of work, Oprian determined that one of the two explanations for the mutations causing CNB was not viable. A sabbatical spent with Prof. Gebhard Schertler at the Laboratory for Molecular Biology in Cambridge, England, was useful in obtaining structures from crystals of the dark and active states of rhodopsin, a protein that is notoriously difficult to crystallize. Dr. **John Lisman**, professor of biology and Volen Center, also spoke about the culmination of many years of research in his talk entitled "CaMKII as a Synaptic Memory Molecule: The Final Key Experiments Fall into Place." Building on the work of many other laboratories that strongly suggests this protein (calcium/calmodulin-dependent kinase II) is the key element in creating memory, Lisman

has recently shown that this chemical switch consisting of fifteen to twenty molecules can remain stable for a century. Using an inhibitor to turn off this switch and reset memory at the synapse, Lisman provided further evidence that this protein in fact is responsible for memory. While each speaker at the Retreat addressed a different kind of complex system, ranging in scale from the molecular (memory) to the global (ecosystems) and artificial (robotics), the talks underscored the progress that has been made in some of the major unsolved problems in neuroscience.

Now completing its seventh year, the *M.R. Bauer Distinguished Guest Lecturer Series* brought Dr. **Hollis Cline** to the annual retreat as its keynote speaker. Dr. Cline is the Charles and Marie Robertson Professor of Neurobiology and Associate Director for Research at the Cold Spring Harbor Laboratory on Long Island, New York. Using the tadpole as a model organism, she studies the retinal projection to the optic tectum, the structure in the mid-brain associated with vision. She is especially interested in how connections are made in the early development of the brain. Her work has shown a surprising result—as growth occurs, neurons continually add new branches, but they also retract many branches in a "trial and error" process. Professor Cline is well

known for having conducted one of the first experiments to visualize the axon, the fiber that conducts impulses away from a neuron, in a living brain. Her highly original work in looking at various forms of plasticity in the brain has helped to change the static picture of dendrites and synapses previously held by many neuroscientists.

There are many ways that sensory activity affects the development of neural circuits, including their growth rate, excitability, and map formation, among others. Professor Cline's talk, entitled "Multiple Activity Dependent Mechanisms Control Visual System Development in *Xenopus* [the tadpole]," focused on a few experiments that looked closely at neurons' growth rate and ability to form synapses, the connections among neurons where memories form and take hold. In early development, there is a large increase in transmissions to receptors at the synapse, which stabilizes them and allows them to function despite larger shifts in electrical activity. Cline has been able to see the entire dendritic arbor, the tree-like branches that extend from the neuron to connect with other neurons, and the axon. What controls the development of the arbor, which becomes more complex over the first several days of the tadpole's life? The dendritic arbor is important because its complexity,

developed in a series of branchings and retractions, will determine the number of inputs or connections from other cells. Professor Cline believes that visual activity itself regulates this process. Does synaptic input promote arbor development or do larger arbors permit the creation of new synapses? Because the growth of dendrites is concurrent with the maturation of the synapse, Professor Cline tried to sort out the mechanism that is driving this process. Her experiments showed that synaptic transmissions, which channel sensory inputs, regulate the growth of arbors. Professor Cline also wanted to know whether synaptic contacts regulate axon development—the "output" side of the story. Using tags to see proteins at the pre-synaptic vesicles, she showed that strong synapses stabilize retracting branches. Branches tend to pull back until they reach a strong synapse, suggesting that synapses strengthened by activity stabilize the axon branch on which they reside. The Retreat audience was particularly impressed by Professor Cline's visual evidence, a series of photographs of living neurons showing growth or retraction.

For more than a decade, the M.R. Bauer Foundation Colloquium and Scientific Retreat have helped to spur exchanges among neuroscientists that have advanced the study of the brain, learning, and memory. Likewise, the M.R. Bauer Distinguished Guest Lecture Series, which for seven years has brought

some of the field's most honored scientists to campus, has greatly benefited our faculty and students. This booklet conveys, in brief abstracts, some of the most exciting work taking place in neuroscience today and demonstrates the diversity of approaches and problems that fall under this broad field. My colleagues and I are delighted to express our sincere gratitude to the M.R. Bauer Foundation for its continuing, generous support that has made these programs possible—and that has fostered the intense conversations that help to advance our work in solving these problems.

Arthur Wingfield, D.Phil.
Nancy Lurie Marks Professor of Neuroscience and Director, Volen National Center for Complex Systems

Yang Dan, Ph.D.

Associate Professor
Department of Molecular and Cell Biology
University of California, Berkeley
Berkeley, California
November 15, 2004

Activity – Dependent Plasticity in the Visual Cortex

Activity-dependent plasticity is essential for the development and function of the nervous system. In mammalian cortex, sensory stimuli play crucial roles in shaping the neuronal circuitry and function, and such plasticity may be largely mediated by activity-dependent synaptic modification. Although at each level—synaptic, circuitry, and functional—cortical plasticity has been studied extensively, the causal relationship between activity-induced modifications at different levels remains to be firmly established. The goal of Dr. Dan's research is to bridge our understanding of cortical plasticity at these levels.

In his talk he described his studies in the past several years on stimulus-induced functional modification in the visual cortex that is believed to be mediated by spike-timing dependent plasticity (STDP) of intracortical connections. In STDP, the direction and magnitude of synaptic modification depend on the relative timing of pre- and postsynaptic spiking.

In the first part, Dr. Dan described the studies done in visual cortical slices, where they characterized the basic STDP learning rule, how it depends on the dendritic location of the synaptic inputs and how complex patterns of spiking activity determine the direction and magnitude of synaptic changes. His studies have also shed some light on the cellular mechanisms underlying this form of synaptic plasticity.

In the second part, he described his attempts to explore the functional significance of STDP in vivo. His experiments include pairing visual and electrical stimulation in the rat visual cortex and using precisely timed visual stimulation to induce changes in visual cortical processing in the rat. In exploring how STDP interact with visual stimuli in the natural environment, they found a novel interaction between motion and position in cortical neurons' receptive field, which can explain a well-known visual illusion in human. Finally, Dr. Dan discussed his recent work on the effect of natural scenes in shaping cortical response properties.

Nancy Kanwisher, Ph.D.

Professor
Department of Brain and Cognitive Sciences
Massachusetts Institute of Technology
Cambridge, Massachusetts
December 6, 2004

fMRI of Visual Recognition

Dr. Nancy Kanwisher, Professor of Brain and Cognitive Sciences at MIT, described some of her recent studies of the neural and cognitive mechanisms underlying human visual perception and cognition. In her previous work, she has investigated object recognition, visual attention, and perceptual awareness, as well as response selection, social cognition and the human understanding of numbers. Kanwisher is best known for her pioneering work that has identified several regions of the human brain that seem to play specialized roles in the perception of specific categories of visual stimuli such as faces, places, and bodies.

Some of Kanwisher's evidence that face perception is mediated by special cognitive and neural mechanisms comes from her functional magnetic resonance imaging (fMRI) studies of the human brain's fusiform face area (FFA) and from behavioral studies of the "face inversion effect." Kanwisher combined these two methods to ask whether face perception mechanisms are stimulus specific, process specific, or both. In those experiments subjects discriminated pairs of upright or inverted faces or house stimuli that differed in either the spatial distance among parts (configuration) or the shape of the parts. The FFA showed a much higher response to faces than to houses, but no preference for the configuration task over the part task. Similarly, the behavioral, face inversion effect was as large in the part task as the configuration task for faces, but absent in both part and

configuration tasks for houses. According to Kanwisher, these findings indicate that face perception mechanisms are not process specific for parts or configuration but are domain specific: that is, they are selective face stimuli per se.

Kanwisher acknowledged that function of the fusiform face area (FFA), a face-selective region in human extra striate cortex, remains a matter of active debate. To bring clarity to the issue, she measured the trial-by-trial correlation between FFA activity measured by functional magnetic resonance imaging (fMRI) and behavioral outcomes in perceptual tasks. Her results show that FFA activation is correlated on a trial-by-trial basis with both detecting the presence of faces and identifying specific faces. However, for most non-face objects (including cars seen by car experts), within-category identification performance was correlated with activation in other regions of the ventral occipitotemporal cortex, not the FFA. These results indicate that the FFA is involved in both detection and identification of faces, but that it has little involvement in within-category identification of non-face objects (including objects of expertise).

Together with her post-doctoral student, Chris Baker, and Eli Pelli of Harvard's Department of Ophthalmology, Kanwisher has explored neural plasticity and reorganization. In these studies she exploited disease-related changes in retinal function that are associated with macular degeneration (MD), the leading cause of visual impairment in

the developed world. MD damages the central retina, obliterating fovea vision and severely disrupting everyday tasks such as reading, driving, and face recognition. In such cases, the macular damage eliminates the normal retinal input to a large region of visual cortex, comprising tens of square centimeters of surface area in each hemisphere, which is normally responsive only to fovea stimuli. Using functional magnetic resonance imaging, Kanwisher and colleagues asked whether this deprived cortex simply becomes inactive in subjects with MD, or whether it takes on new functional properties. In two adult MD subjects with extensive bilateral central retinal lesions, Kanwisher and colleagues found that parts of visual cortex (including primary visual cortex) that normally respond only to central visual stimuli are strongly activated by peripheral stimuli.

Such activation was not observed (1) with visual stimuli presented to the position of the former fovea, or (2) in control subjects with visual stimuli presented to corresponding parts of peripheral retina. These remarkable results demonstrate large-scale reorganization of the brain and of visual processing in MD, and will likely prove important in any effort to develop new strategies for rehabilitation of MD subjects.

David Rosenfield, M.D

Director, Speech and Language Center
Neurological Institute
The Methodist Hospital/ Baylor
College of Medicine
Houston, Texas
March 14, 2004

A Neuroscience Perspective on Stuttering

Stuttering afflicts one percent of the world's adult population. A ten-year-old child who stutters might be terrified to speak in front of his class, yet is fluent when singing, despite similar embarrassment. Stutterers are fluent when singing. This disrupted speech motor output of stuttering is not random and probably reflects disturbance in auditory feedback. An improved understanding of this disruption in speech (motor) output would improve our understanding of language processing. Dr. Rosenfield presented current research, including an animal model of stuttering. This model focuses on phonotory iterations in Zebra finches and provides insight into this disorder.

Steven Roper, Ph.D.

Professor
Department of Physiology and Biophysics
University of Miami School of Medicine
Miami, Florida
May 2, 2005

Signal Processing and Synaptic Intercourse in the Mammalian Taste Bud: Nontraditional Transmitter Mechanisms

Taste bud cells communicate with sensory afferent fibers and may also exchange information with adjacent cells. Indeed, communication between taste cells via conventional and/or novel synaptic interactions may occur prior to signal output to primary afferent fibers. Dr. Roper presented results showing that it is now possible to measure real time release of synaptic transmitters during taste stimulation of taste buds. His data provide strong evidence that serotonin, ATP, and glutamate play a role in cell-to-cell signaling in taste buds and sensory output from these gustatory end organs.

These findings lend themselves to a working hypothesis that potentially dispels a disquieting controversy between recent findings at the molecular and cellular levels in taste. Namely, molecular studies have led some investigators to conclude that taste is encoded as a "labeled line," yet findings at the cellular level that indicate taste is a "combinational code." These conflicting ideas may not be as opposing as has been believed to date. Dr. Roper's findings can explain how this conundrum is resolved.

**The M.R. Bauer
Distinguished Lecturer
Series Summaries
2004-2005**

Introduction

One of the highlights again this year has been the M.R. Bauer Distinguished Guest Lecturer Series. This program, now completing its seventh year, brought Hollis Cline to campus, a well-known neuroscientist and the Associate Director of Research at Cold Spring Harbor.

Dr. Cline spent a week at Brandeis and also delivered the keynote address at our Scientific Retreat. Dr. Cline's schedule for the week was full of meetings with graduate students, postdoctoral fellows, and faculty, and she spent time visiting many neuroscience laboratories. Feedback from our students continues to clearly indicate that it is a significant privilege to have world-class scientists such as Dr. Cline spending this amount of time on campus, getting to know the students, and providing invaluable advice to these younger scientists. These weeks are very busy, informative, and enjoyable for all.

Hollis Cline, Ph.D.

Charles and Marie Robertson
Professor at Cold Spring Harbor and
Associate Director for Research at
Cold Spring Harbor
Cold Spring Harbor, New York

**Multiple Activity
Dependent Mechanisms
Control Visual System
Development in Xenopus**

Sensory input into the brain is essential for organizing brain connectivity and circuit function during development and for modifying neuronal circuits with learning in the mature nervous system. Dr. Cline's lab is working on the cellular and molecular mechanisms that operate to establish and modify brain connections during development. Nervous system dysfunction may arise from failure of these mechanisms to operate during development or in the mature nervous system. Her lab addresses this issue by examining the structural and functional development of the visual system in amphibian tadpoles. These animals are transparent which allows one to observe directly the development of the brain in living animals. In addition, they assessed neuronal function using electrophysiological assays of synaptic connectivity and synaptic plasticity. They combined these studies with gene transfer methods, which allowed them to test the function of genes of interest in brain development. One of the highlights of Dr. Cline's recent research was the demonstration that glutamate receptor activity following visual stimulation is required for the normal development of topographically organized connections from the eye to the central nervous system. She further demonstrated that visual experience enhances the growth rate of dendritic arbors and visual responsivity of postsynaptic optic tectal neurons. These studies laid the groundwork for their current work on specific mechanisms by which brain connectivity develops in the intact animal.

**The M.R. Bauer
Foundation
Scientific Retreat 2005**

The 2005 Volen National Center for Complex Systems retreat was held at the Charles River Museum of Industry in Waltham, Massachusetts. This museum was an undiscovered local gem for many of the guests, and its exhibits of local history, clock works, trains, and other machinery added to the education and pleasure of us all. In addition to our keynote speaker, Hollis Cline, five Brandeis faculty spoke about a variety of topics. The interdisciplinary nature of this retreat is a fine example of the scientific interdisciplinary efforts of the Volen Center. The day was a complete success, from the well-received lectures, to the setting, food and musical entertainment which was provided by a neuroscience graduate student and a postdoctoral fellow.

**Volen National Center
for Complex Systems
Annual Retreat, 2005**

**“From Molecules
to Robots”**

Monday, April 25th, 2005
Charles River Museum of Industry
Waltham, Massachusetts

10:45am

Welcoming Remarks

Arthur Wingfield, D.Phil.

Nancy Lurie Marks Professor of
Neuroscience and Director, Volen
National Center for Complex
Systems

Jeaneatte McCarthy

Mayor of Waltham

11:00am

Daniel Perlman, Ph.D.

“A Brief Ecological History of
Boston’s Suburbs”
Assistant Professor of Biology
Brandeis University

11:45am

Susan Birren, Ph.D.

“From Heart to Brain: Controlling
Neuron Development and Function”
Associate Professor of Biology and,
Volen National Center for Complex
Systems
Brandeis University

12:30pm Lunch

1:30pm

Jordan Pollack, Ph.D.

“Recent Progress in
Co-evolutionary Learning”
Professor of Computer Science
and Volen National Center for
Complex Systems
Brandeis University

2:15pm

Daniel Oprian, Ph.D.

“Mutation of Rhodopsin in Health,
Disease, and Sabbatical Leave”
Louis and Bessie Rosenfield
Professor of Biochemistry and
Volen National Center for Complex
Systems
Brandeis University

3:00pm Afternoon Break

3:30pm

John Lisman, Ph.D.

“CaMK11 as a Synaptic Memory
Molecule: the Final Key
Experiments Fall into Place”
Professor of Biology and Volen
National Center for Complex
Systems and Chair,
Neuroscience Program
Brandeis University

4:15pm

Hollis Cline, Ph.D.

“Multiple Activity Dependent
Mechanisms Control Visual
System Development in
Xenopus”
Charles and Marie Robertson
Professor at Cold Spring Harbor
and, Associate Director for
Research at Cold Spring Harbor

5:00pm Poster Session

6:00pm Dinner and Music

Daniel Perlman, Ph.D.

Assistant Professor of Biology
Brandeis University
Waltham, Massachusetts

A Brief Ecological History of Boston's Suburbs

The Volen Center focuses on a wide variety of complex systems and Dr. Perlman proposed that ecosystems represent another type of complex system worth studying. If we consider just a single place on the Earth's surface—such as eastern Massachusetts—it quickly becomes clear just how many factors have affected the ecological landscape that we see today.

It is relatively easy to see many of the ecological and geological histories that have created our region. For example, with little effort one can find throughout the Boston area examples of Roxbury Puddingstone (or conglomerate), a rock formation that dates from the pre-Cambrian time over 500 million years ago, when multi-celled animals were first appearing on the planet. However, our region is not uniform in its geological history. The eastern half of the state arose from the southern continent Gondwana or island arcs near Gondwana, while the western half of the state developed from the northern continent Laurentia. In addition, although the bedrock of most of the state is hundreds of millions of years old, Cape Cod is some of the youngest land on the planet: it was deposited by the most recent glaciers to cover our region. When the glaciers eventually withdrew about 12-14,000 years ago, they left behind the Cape as piles of sand and rock that had been brought in from the north. Thus, within a space of less than a hundred miles we find three very different geological origins strewn across the state.

Once the geological changes settled down, and as the glaciers withdrew, the most recent set of ecological changes (those we can see best) began. As the glaciers receded and left the barren landscape that would become Massachusetts uncovered, the land was first colonized by plants and lichens similar to those of today's Arctic tundra. Just a couple of thousand years later humans began to colonize the area; because humans inhabited Cape Cod less than 2,000 years after it was formed, nearly all of the Cape's existence has included humans as a major influence.

The single most striking ecological feature of the eastern Massachusetts landscape since the glaciers left has been drastic change. As the edge of the glaciers moved further north, a series of plant communities migrated into the region and then passed on to the north. After the tundra plants passed through, the land was covered by a succession of spruce forests, pine forests, and deciduous forests. About 5,000 years ago the hemlocks that had been a dominant part of the forest suffered a rapid and calamitous decline that lasted a thousand years, and chestnut trees, which became dominant over much of the region, only arrived about 3,000 years before present. Just 2,000 years later, Native Americans began practicing agriculture in earnest across much of the region, and several hundred years later Europeans began to write their own ecological changes on the landscape, clearly most of it by about 1850. From the written history of the nearly 400 years since

European settlement, we also know that our region is regularly buffeted by massive hurricanes that knock down large swathes of forest, opening the landscape up for regrowth and regeneration. In short, the unbroken, untouched forest primeval of our histories and imaginations was not even fully assembled until the era of the Trojan War, and it has never been as unchanging and pristine as we once thought.

In the past century and a half, as the wave of farming moved west, our forests began to recover so that today most of Massachusetts is heavily forested. Human commerce has vastly increased the rate of movement of plants and animals across the planet. However, we have seen Chestnut blight turn one of our most magnificent tree species into a band of tiny, shrubby fugitives that exist for a few years until they succumb to the fungus; the Dutch elm disease has wiped out the American elms that graced our forests and so many of our city streets; and many other exotic caterpillars such as the gypsy moth and winter moth attack the deciduous trees of our forests.

Although Massachusetts is not known globally for its biological diversity, even this brief look gives a sense of the ecological and geological complexity of our small corner of the world. Our forests—even the small Sachar Woods of the Brandeis campus—reveal this history to those who take the time to look.

Susan Birren, Ph.D.

Associate Professor of Biology
Volen National Center for Complex
Systems
Brandeis University

From Heart to Brain: Controlling Neuron Development and Function

Cardiac function is modulated by norepinephrine release from innervating sympathetic neurons. These neurons also form excitatory connections onto cardiac myocytes in culture. Dr. Birren's lab has shown that the neurotransmitter properties of these target connections are modulated by target-derived neurotrophic factors. Nerve growth factor (NGF) increases the activity-dependent release of norepinephrine from sympathetic synapses, acutely potentiating excitatory transmission. In contrast, brain-derived neurotrophic factor (BDNF) regulates the release of a second neurotransmitter, acetylcholine, leading to a rapid shift to inhibitory cholinergic transmission in response to neuronal stimulation. These data indicate that sympathetic control of cardiac function can be rapidly modulated by the availability of specific factors from the target. The actions of BDNF are mediated through the p75 neurotrophin receptor. P75^{-/-} neurons do not release acetylcholine in response to BDNF, while neurons overexpressing p75 show increased cholinergic transmission. These results demonstrate a novel role for p75 in modulating the release of distinct neurotransmitter pools, resulting in a functional switch between excitatory and inhibitory neurotransmission in individual neurons. The p75 receptor also regulates neurotransmitter properties in the central nervous system. Interactions between GABAergic and cholinergic neurons define the output of basal forebrain projections and thus contribute to the development and functional properties of cortical circuits. They have shown that the p75 receptor influences the relative number of

basal forebrain cholinergic and GABAergic neurons. In the absence of p75, GABAergic neurons develop, but GABAergic development is no longer affected by neurotrophins. Since p75 is not actually expressed in the GABAergic population, this defines a new, non-cell autonomous mechanism of p75 action. Neighboring cholinergic neurons do express p75 and they have demonstrated that neurotrophin activation of cholinergic p75 results in release of a soluble factor that modifies neurotrophin responses of nearby neurons. Thus, p75-mediated interactions between cholinergic and GABAergic neurons, together with activity-dependent responses, regulate the balance of excitatory and inhibitory components of basal forebrain circuits.

Jordan Pollack, Ph.D.

Professor of Computer Science
and Volen National Center for
Complex Systems
Waltham, Massachusetts

Recent Progress in Co-evolutionary Learning

For many years Dr. Pollack's lab has been working on electronic and software systems, which can

learn and develop on their own in open-ended innovative ways. This is based on understanding and mimicking natural co-evolution. However, in nature, co-evolution refers to the contingent development between species. For machine learning, co-evolution has come to mean the search "arms-race" type phenomena, which can lead multiple agents to develop through their own interaction, without the need for an intelligent designer. Most work in machine learning, for example using Neural Networks, involves very careful design of data representations, which are tuned to a carefully designed learning environment. In co-evolution, the set-up is usually as a set of players to a "game" who start with only the rules and must develop strategy or tactics through interaction. Generally, this interaction is a competition for limited resources such as places in a fixed-sized population. His lab has had some success, for example in optimization, such as discovering the best sorting networks and cellular automata rules, as well as in three generations of automatically designed robots.

However, as they developed these co-evolutionary learning algorithms, they discovered that despite many successes, certain phenomena arise repeatedly to prevent continuous innovation. These phenomena are familiar from economic markets, and include winner-take-all monopolies, boom/bust cycles, and stable mediocre oligarchies (groups of players who tacitly collude to protect each other from further innovation).

Dr. Pollack's group has been developing theoretical incentive frameworks in which self-interested adaptive agents can keep learning, including the development of multi-objective or Pareto Coevolution, the discovery of new dimensions along which to compare evolving agents, and a central metaphor "The Teacher's Dilemma," which replaces competition with symmetric teacher-student interactions. The Teacher's Dilemma provides a scientific basis for rewarding teachers in a different fashion than competition or altruism. This leads to new mechanism designs in which self-interested agents end up forming learning communities which don't suffer from the equilibria phenomena.

The first major practical application of this work has been the development of scaleable peer-to-peer learning environments for children. These are multi-player video games, but the highest scores accrue to players who provide appropriate challenges to each other, turning students into each other's teachers. Dr. Pollack's group launched the first online spelling bee

www.spellbee.org in 2004 and now have 25,000 members. Initial results show that a majority of students adapt to the Teacher Dilemma utility and many face gradually increasing challenges from other students. They have just launched www.patternbee.org and www.moneybee.org in which students present each other with geometric and algebraic problems.

Daniel Oprian, Ph.D.

Louis and Bessie Rosenfield
Professor of Biochemistry and Volen
National Center for Complex Systems
Brandeis University
Waltham, Massachusetts

Mutation of Rhodopsin in Health, Disease, and Sabbatical Leave

Congenital night blindness (CNB) affects retinal rod photoreceptor cells and is expressed as an inability to see under dim light conditions. Three different mutations in rhodopsin have been shown to cause autosomal dominant CNB in humans; Gly90!Asp, Thr94!Ile, and Ala292!Glu. While there is general agreement that the disease is caused by inappropriate stimulation (and consequent desensitization) of rod cells, there is some controversy regarding the source of the stimulatory signal. Two models have been proposed. In Model I, the stimulatory signal is proposed to come from the constitutively active apoprotein, or opsin, forms of the mutant rhodopsins. This model was originally proposed for the A292E and G90D mutants, but it is now known that all three mutant opsins (including the more recently identified T92I mutant) are constitutively active under *in vitro* assay conditions. In Model II, the stimulatory signal is postulated to result from increased thermal isomerization of the 11-*cis*-retinal chromophore in the holoprotein, or pigment, forms of the mutant rhodopsins to generate a metarhodopsin II intermediate which results in desensitization of the photoreceptor cell. Model II was originally proposed for the mutant G90D on the basis of theoretical considerations and was subsequently promoted on the basis of FTIR studies of the recombinant mutant.

These two models are similar in that both invoke an active species that would be present at vanishingly small concentrations within the rod photoreceptor cell (the dark-adapted thresholds of G90D patients are elevated by 3 log units, but in the highly-sensitive rod cell containing 10^8 – 10^9 rhodopsin molecules this level of sensitivity is equivalent to what would be observed from adaptation to a light stimulus in which there were only about 10 photoisomerization events per rod cell). The two models differ, however, in terms of the chemical makeup of the active species, and they have exploited this difference to design a simple experimental test to distinguish these two models using isolated rod photoreceptor cells from transgenic *xenopus laevis* and exogenously added 11-*cis*-retinal. According to both models, they expect rod cells from the CNB mutants to exhibit significant desensitization of the light-evoked currents (intensity-response curve shifted to higher light intensity and more rapid flash-response kinetics). In Model I, the active signal comes from the apoprotein; 11-*cis*-retinal would decrease the equilibrium concentration of opsin, turn off the constitutive activity, and rescue the wild-type phenotype (intensity-response curve shifted to lower light intensity and slowed flash-response kinetics). In Model II, the active signal comes from the holoprotein; added 11-*cis*-retinal would have no effect.

expected of CNB mutants. The cells are then incubated with exogenously added 11-*cis*-retinal and the electrical recordings repeated to determine if the cells remain desensitized or if they recover wild-type sensitivity. If Model II were responsible for the CNB phenotype, thermal isomerization of the chromophore rhodopsin should be unaffected by added 11-*cis*-retinal, and we would expect the cells to remain desensitized after treatment with retinal. In contrast, if Model I were responsible for the CNB phenotype, the constitutively active mutant opsin should be converted to the inactive rhodopsin form following incubation with retinal, and we would expect the cells to exhibit wild-type sensitivity following incubation with retinal.

They showed here that the rod cells from all three CNB mutants are desensitized as isolated but recover wild-type sensitivity following incubation with 11-*cis*-retinal. These data are inconsistent with Model II and eliminate thermal generation of metarhodopsin II from rhodopsin as a source of the desensitized CNB phenotype. Furthermore, while the data do not prove Model I, they are exactly what would be expected from that model in which constitutively active mutant opsin causes the desensitization of the CNB photoreceptor cells.

Thus, the experimental design is as follows. Rod photoreceptor cells are isolated from transgenic frogs containing rhodopsin CNB mutations. Suction micropipette recordings are used to show that the cells display the desensitized response to light

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CaMK11 as a Synaptic Memory Molecule: the Final Key Experiments Fall Into Place

An important unsolved problem in Neuroscience is the molecular basis of memory. This problem is being extensively studied in many laboratories using LTP of hippocampal synapses as a model system. In this LTP model, synapses are briefly stimulated with high frequency stimulation. As a result, they undergo a persistent strengthening that can last for years. Dr. Lisman has been investigating the molecular basis of this strengthening. Considerable evidence has accumulated for a role for the protein kinase, CaMKII, in this process. This kinase is persistently activated after LTP. Moreover, when introduced into neurons it can potentiate synapses in a way that occludes with LTP. They have now investigated whether the persistent activation of CaMK11 has a role in the persistence of LTP. He finds that application of a CaMK11 inhibitor can reverse saturated LTP. Importantly, after such reversal, additional LTP can be induced. Taken together with previous work, these results make a strong case for CaMK11 as a key molecule underlying synaptic memory.

The text of this summary of the Bauer Foundation series, along with summaries from previous years, can be found at: www.bio.brandeis.edu/bauer/previous.html.

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