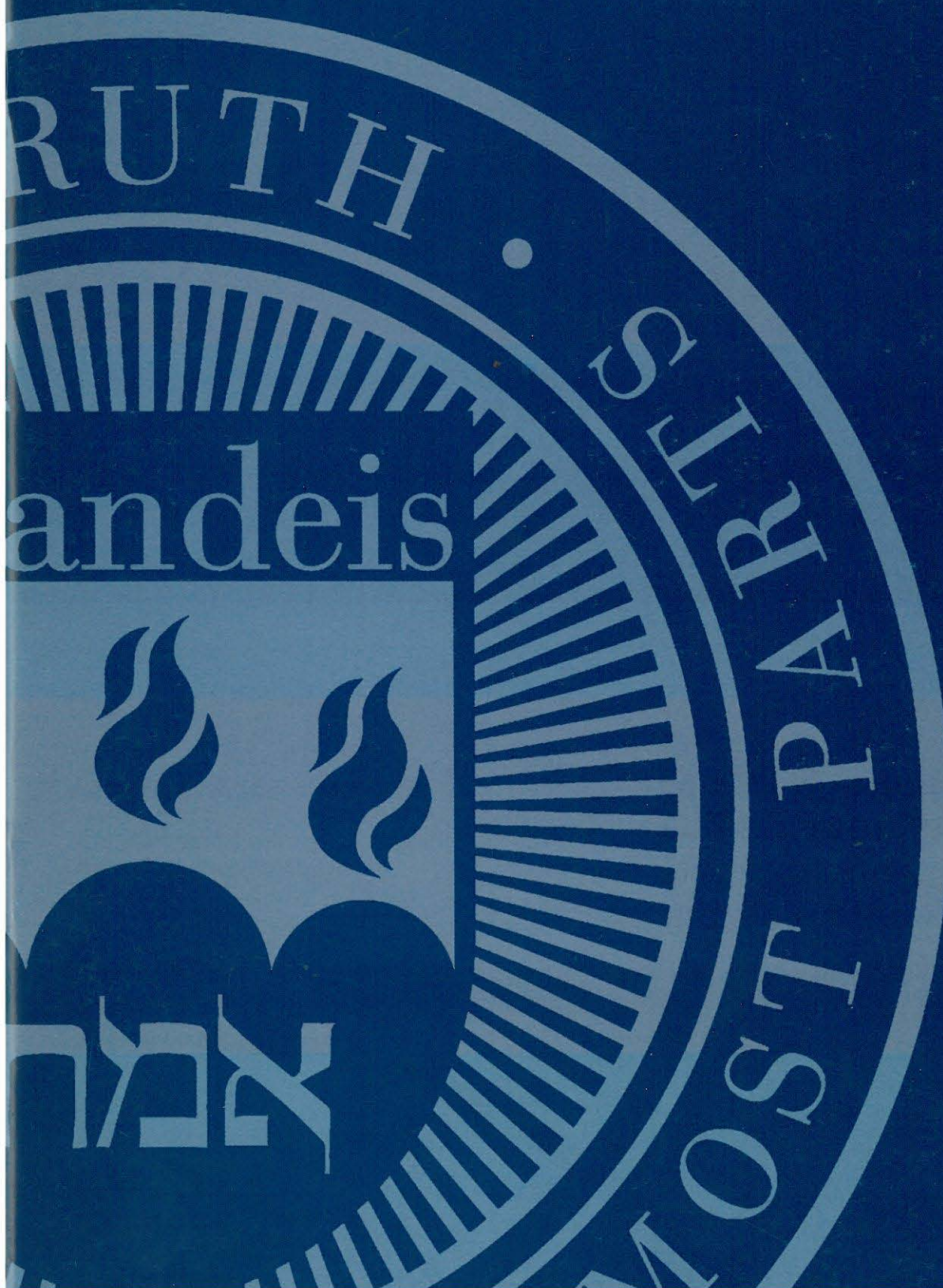

Brandeis University

Benjamin and Mae Volen National
Center for Complex Systems

August 2007

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



The M. R. Bauer Foundation Colloquium Series, Distinguished Lecturer Series, and Scientific Retreat 2006–2007 Summary

Brandeis University

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

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Introduction

The 2007 Bauer Foundation Colloquium Series, Annual Scientific Retreat, and Distinguished Guest Lecturer Series

It is my pleasure to provide a description of this year's proceedings of the M. R. Bauer Foundation Colloquium Series, Scientific Retreat, and Distinguished Guest Lecturer Series at Brandeis University's Volen National Center for Complex Systems. The foundation has supported these activities for thirteen years, and your generosity has allowed the Volen Center to present emerging knowledge in the rapidly evolving field of neuroscience to a broad audience in the scientific community. In the 2006–2007 academic year, we had the privilege of organizing outstanding and informative lectures and informal interactions that showcased leading-edge research in neuroscience. On behalf of my colleagues at Brandeis University, I would like to express our extreme gratitude to the M. R. Bauer Foundation for its long-standing commitment to the Volen Center and neuroscience at Brandeis.

The 2006–2007 M. R. Bauer Colloquium Series included seven scientists who are highly regarded for their work in neuroscience and who conduct innovative research at prestigious universities, medical schools, and research institutes. **S. Murray Sherman**, PhD, chairman of the Department of Neurobiology, Pharmacology, and Physiology at the University of Chicago, spoke on the topic "The Role of the Thalamus." Dr. Sherman's laboratory studies issues of thalamic functional organization and thalamocortical relationships. Dr. Sherman and his colleagues use a broad interdisciplinary approach, attempting to answer the same or closely related questions with several different techniques that involve neuroanatomical, neurophysiological, and behavioral methods. **Adrian Bird**,

PhD, of the Wellcome Trust Center for Cell Biology at the University of Edinburgh, delivered a talk on "DNA Methylation and Disease." The talk focused on Rett Syndrome (a severe inherited neurological disorder that affects girls), and whether it is irreversible. Dr. Bird's research group is interested in the structure and function of the mammalian genome, and in particular the role of DNA methylation. The third Bauer Colloquium speaker was **Gordon Fain**, PhD, Department of Physiological Science at UCLA. Dr. Fain discussed "Light, Calcium, and the Death of Photoreceptors." This talk featured his laboratory's research on calcium as a second messenger in photoreceptor adaptation. **David Lewis**, MD, director of the Translational Neuroscience Program at the University of Pittsburgh, discussed the pathogenesis of schizophrenia in his talk "Dissecting the Disease Process of Schizophrenia: the Role of Cortical GABA Neurons." The Translational Neuroscience Program aims to understand the neurobiological basis for complex human cognitive and emotional functions. The program also examines the manner in which alterations in the brain give rise to the types of disturbances in these functions that characterize certain psychiatric disorders.

The fifth Bauer Colloquium speaker was **Larry Benowitz**, PhD, director, Laboratories for Neuroscience at Children's Hospital in Boston, Massachusetts. The title of Dr. Benowitz's talk was "Rewiring the

CNS after Injury," and he spoke about the implications of spinal cord injury, stroke, and damage to the optic nerve. He noted that, when properly stimulated, mature CNS neurons can switch into an active state and regenerate their axons *in vivo*. Dr. Benowitz's research focuses on restoring nerve function lost as a consequence of stroke or injury. **Julie Kauer**, PhD, Department of Molecular Pharmacology, Physiology, and Biotechnology at Brown University, presented on "LTP at GABAergic Synapses in the Reward Pathway." Dr. Kauer's laboratory focuses on understanding molecular mechanisms involved in information storage and modulation of excitability in the brain, using electrophysiological techniques in brain slices. These efforts are concentrated in two brain regions: the hippocampus and the ventral tegmental area (VTA). The final colloquium speaker was **Mark Bear**, PhD, Picower Professor of Neuroscience and director of the Picower Institute for Learning and Memory at MIT. Dr. Bear is also a Howard Hughes Medical Institute Investigator. He discussed "Mechanisms for Visual Cortical Plasticity," offering insights on how synapses in the brain change and on identifying general principles of cortical plasticity. Dr. Bear's laboratory seeks to understand how synapses in the cerebral cortex are modified by experience.

Now in its ninth year, the M. R. Bauer Distinguished Guest Lecturer Series included two elite scientists, **Richard Tsien** and **Tobias Bonhoeffer**, who came to campus for extended visits. Richard Tsien, PhD, Department of Molecular and Cellular Physiology in the School of Medicine at Stanford

University, spoke on the topic "Deciphering Fundamental Units of Neural Communication." Dr. Tsien's laboratory studies how the location and identity of presynaptic calcium channels are regulated. Voltage-gated Ca²⁺ channels provide the critical link between the firing of a presynaptic nerve terminal and its release of neurotransmitters. The Ca²⁺ channels must be positioned very close to sites of vesicle fusion, and they come in diverse forms with distinct activity dependence; responsiveness to GABA, dopamine, acetylcholine, and other neuromodulators; and susceptibility to neurological disorders such as migraine, ataxia, or dystonia. Dr. Tsien's working hypothesis involves molecular "slots" for particular types of channels. Slots regulate the mix of channel types and also help explain how defective channels might displace normal ones in genetically dominant disorders. **Tobias Bonhoeffer**, PhD, Max Planck Institute of Neurobiology, focused his presentation on "How Activity Changes Synapses in the Mammalian Brain." Dr. Bonhoeffer's laboratory investigates the fundamental principles of synaptic plasticity at a number of different levels, ranging from molecular approaches to studies of the intact nervous system. Recent results from his lab have shown that synaptic plasticity is accompanied by structural changes of dendritic

spines. They have demonstrated the importance of neurotrophins in synaptic plasticity and have revealed the detailed structure of functional maps in the visual cortex.

The 2007 Volen Center Scientific Retreat focused on "Expanding Horizons" and took place at the Endicott House in Dedham, Massachusetts. The event was attended by some one hundred faculty members, staff members, and students, including visitors from other institutions. Five emerging young scientists from Brandeis University spoke about topics that ranged from cryo-electron tomography to human behavior. **Daniela Nicastro**, PhD, Assistant Professor of Biology, discussed the principle of electron tomography and this concept's limitations, in her talk "The New Ice Age: Cryo-Electron Tomography." **Douglas Theobald**, PhD, assistant professor of biochemistry, presented ongoing research that involves superpositioning of biological structures in his presentation "Procrustes Meets Theseus: Maximum Likelihood Superpositions." In addition, **Michael Hagan**, PhD, assistant professor of physics, focused on dynamical processes in organisms, as well as what features of capsid proteins make virus assembly robust. His talk was titled "Dynamical Pathway for Viral Capsid Assembly." **Paul Garrity**, PhD, associate professor of biology, provided an insightful presentation, "Feeling the Heat: Thermosensory Behavior in *Drosophila*," on the molecular mechanisms by which animals detect temperature and on how animals have evolved sophisticated thermosensory

systems. The final talk was given by **Angela Gutches**, PhD, assistant professor of psychology, on "Memory Specificity with Age." Dr. Gutches spoke about her research regarding the effect of age and adult aging on memory and cognition.

The Brandeis and broader scientific communities have greatly benefited from the M. R. Bauer Foundation programs. In the past thirteen years, the colloquium and scientific retreat have drawn eminent neuroscientists who share the results of their cutting-edge research with students and faculty alike. The M. R. Bauer Distinguished Guest Lecturer Series, over the past nine years, has included internationally respected scientists who are promoting discussion and exchange of ideas to advance the study of neuroscience. The publication of these proceedings is a critical component of the Volen Center's attempts to encourage scientific collaboration and conversation. I would like to extend my deep appreciation—and that of my colleagues—to the M. R. Bauer Foundation.

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

Murray Sherman, PhD

Professor
Department of Neurobiology,
Pharmacology, and Physiology
University of Chicago
Chicago, Illinois
November 20, 2006

The Role of the Thalamus: Relay Functions and More

The LGN and pulvinar (a massive but generally mysterious and ignored thalamic relay) are examples of two different types of relay: the LGN is a *first-order* relay, transmitting information from a subcortical source (retina), while the pulvinar is mostly a *higher-order* relay, transmitting information from layer 5 of one cortical area to another area. First- and higher-order thalamic relays can also be recognized for the somatosensory and auditory thalamic systems, and this division of thalamic relays can also be extended beyond sensory systems. Thus the first- and higher-order thalamic equivalents of the somatosensory and auditory systems are, respectively, the ventral posterior nucleus and the posterior medial nucleus (somatosensory), and the ventral (versus dorsal) portion of the medial geniculate nucleus (auditory). Other thalamic nuclei have also been placed into this framework, and so the medial dorsal nucleus is mostly higher-order, while the ventral anterior and ventral lateral nuclei seem to be a mosaic of the first- and higher-order relays. It now seems clear that most of the thalamus is composed of higher-order relays.

Higher-order relays seem especially important to general corticocortical communication, and this view challenges and extends the conventional view that such communication is based mainly on direct corticocortical connections. In this sense, any new information reaching a cortical area, whether from a subcortical source or another cortical area, benefits from a thalamic relay. Thus the thalamus is not just a simple relay responsible for getting peripheral information to the cortex. Instead, it provides a behaviorally relevant, dynamic control over the nature of information relayed, and it also plays a key role in basic corticocortical communication.

Adrian Bird, PhD

Professor
Wellcome Trust Centre for Cell Biology
University of Edinburgh
Scotland, United Kingdom
January 22, 2007

DNA Methylation and Disease

The DNA of vertebrate animals is covalently modified by methylation of the cytosine base in the dinucleotide sequence 5'CG3'. In mammals, DNA methylation patterns are established during embryonic development and maintained by a copying mechanism when cells divide. The heritability of DNA methylation patterns allows epigenetic marking of the genome to be stable through multiple cell divisions and therefore constitutes a form of cellular memory. The existence of DNA methylation patterns raises two important questions: 1) How are the patterns formed? 2) How are they read to generate biological outcomes? We have focused on the second question and have identified a set of proteins that recognize and bind to methylated sites in the genome. Most of these proteins are transcriptional repressors that recruit corepressor complexes, which modify chromatin structure to ensure gene silencing.

To understand the biology of these proteins and their role in human disease, we have created mouse gene knockouts for methyl-CpG binding domain (MBD) proteins and identified cases of gene misregulation that can be attributed to the absence of one of these proteins. For example, efficient repression of the *Xist* gene on the active X chromosome and of exocrine pancreatic enzyme genes in the mouse colon requires MBD2. Interestingly, despite their common DNA binding sites, these proteins apparently do not substitute for one another. Thus, it seems that the bona fide target genes regulated by each

methyl-CpG binding protein are distinct. Our work has begun to reveal the molecular basis for this specificity by establishing significant DNA preferences in addition to the requirement for methyl-CpG.

The MBD protein MECP2 is of particular interest as mutations affecting its gene are the primary cause of Rett Syndrome, which is the most common inherited form of mental retardation affecting human females. Delayed-onset symptoms include developmental delay, loss of purposeful limb use, and breathing abnormalities. As there is no obvious neurodegeneration in postmortem brains of RTT patients, the question of reversibility arises and is of obvious relevance for therapeutic approaches to RTT. We earlier created a mouse model for RTT that lacks an intact *Mecp2* gene and mimics several features of the disorder, including late onset. Using a mouse with an *Mecp2* allele that can be conditionally activated, we asked whether neuronal defects can be rectified if MeCP2 is provided *de novo* after abnormal neuronal morphology and symptoms have arisen. The results demonstrate that most or all symptoms are in fact reversible. In addition, a deficit in long-term potentiation in the hippocampus is abolished by late reintroduction of MeCP2. These findings have obvious implications for future therapeutic approaches to this disorder and they raise the possibility that MeCP2 is required to maintain gene expression programs in mature neurons.

Gordon Fain, PhD

Professor
Departments of Physiological Science and
Ophthalmology
University of California Los Angeles
Los Angeles, California
January 29, 2007

Light, Calcium, and the Death of Photoreceptors

Exposure of the photoreceptors of the eye to light can produce retinal degeneration. I will describe early experiments showing that even moderate illumination can do this, provided it is given continuously. Apoptosis is not triggered by the light *per se*—that is, by local heating or ultraviolet light damage—but rather by continuous activation of the transduction cascade. We know this, since mice lacking the G protein transducin, which is essential for cascade activation, do not show degeneration in continuous light. This same mechanism is responsible for degeneration during vitamin A deprivation: in the absence of vitamin A (and thus 11-*cis* retinal, the visual chromophore), rhodopsin is noisy and activates the cascade much like constant light. Degeneration during vitamin A deprivation is again blocked in mice lacking the G protein transducin. The mechanism of degeneration is unknown, but recent experiments suggest that continuous activation of the cascade may produce death by decreasing the Ca^{2+} to a very low level and keeping it there for a long period of time. Since low Ca^{2+} can cause degeneration of neurons, it seems likely that a similar mechanism may be responsible for photoreceptor apoptosis. We think this mechanism not only is important for light damage and vitamin A deprivation but possibly represents an important pathway for cell death in inherited retinal disease.

David Lewis, PhD

Professor
Department of Psychiatry
University of Pittsburgh
Pittsburgh, Pennsylvania
February 12, 2007

Dissecting the Disease Process of Schizophrenia: Role of Cortical GABA Neurons

Critical cognitive deficits in schizophrenia, such as impairments in working memory (the ability to transiently keep in mind a limited amount of information in order to guide thought or behavior) are associated with dysfunction of the dorsolateral prefrontal cortex (DLPFC). Postmortem investigations indicate that these cognitive deficits might reflect alterations in the expression of certain genes in specific populations of GABAergic, inhibitory neurons in the DLPFC. In particular, the specific combination of gene expression abnormalities seen in illness converge on the idea that the synthesis of GABA is reduced in the chandelier class of GABA neurons that furnish inhibitory inputs exclusively to the axon initial segment of excitatory pyramidal neurons. This deficit in GABA neurotransmission is associated with an up-regulation of GABAA receptors that contain alpha 2 subunits, which are preferentially localized to pyramidal neuron axon initial segments. Chandelier neurons play a critical role in regulating the synchronization or timing of pyramidal neuron firing during working memory. Thus, these findings suggest that the alterations in chandelier neurons in schizophrenia represent a pathological entity that gives rise to the disturbances in neural synchrony observed clinically in association with working memory impairments in schizophrenia. Reduced neurotrophin signaling via the trkB receptor appears to be a pathogenetic mechanism underlying these abnormalities. Parallel studies in genetically engineered mice support these conclusions. Together, these findings suggest that a medication that enhances GABAergic neurotransmission only at pyramidal neuron axon initial segments and that preserves the normal timing of chandelier neuron activity would improve working memory function and clinical outcome in individuals with schizophrenia.

Larry Benowitz, PhD

Director
Laboratories for Neuroscience
Research in Neurosurgery
Children's Hospital
Boston, Massachusetts
February 26, 2007

Rewiring the CNS after Injury

Damage to the CNS can result in devastating and often permanent losses of sensory, motor, cognitive, and/or autonomic functions. This poor outcome is due in part to the limited capacity of the CNS to regenerate: few neurons that die are replaced; neurons that remain alive but whose axons are injured cannot regenerate their connections; and undamaged neurons have only a limited ability to form new connections to compensate for ones that have been lost. Our lab has been investigating basic mechanisms that underlie the growth of neural connections, and applying insights from this work to improve functional outcome after CNS injury. In the optic nerve, a CNS pathway in which injured axons normally show no capacity to regrow, activating macrophages in the eye causes the main projection neurons of the eye, the retinal ganglion cells (RGCs), to switch into an active growth state and extend lengthy axons through the optic nerve. This growth requires mannose (a normal constituent of the vitreous); an agent to elevate intracellular cAMP; and oncomodulin, which is a newly discovered polypeptide growth factor that is secreted by macrophages and other cells. Oncomodulin is an atypical Ca^{2+} -binding protein that binds to a high-affinity receptor on RGCs and stimulates more extensive outgrowth than other known trophic factors. If, at the same time, RGCs are transfected with a gene that renders them

unresponsive to inhibitory signals associated with myelin and the glial scar, regeneration is enhanced greatly. Axon outgrowth in this and many other systems is mediated via Mst3b, a neuron-specific homolog of a kinase that controls budding in yeast. Mst3b can be inhibited with the purine analog 6-TG and activated with the purine nucleoside inosine. Blocking Mst3b function or expression suppresses axon growth in culture and *in vivo*. Conversely, activating this kinase *in vivo* improves anatomical rewiring and functional outcome after spinal cord injury or stroke. Combined treatments to activate neurons' growth program while counteracting inhibitory signals enhances rewiring and behavioral outcome to an even greater extent. Such combinational treatments fully restored functional use of the forepaw contralateral to a damaged motor cortex in rats. These and related discoveries may someday enable us to improve functional outcome after CNS injury.

Julie Kauer, PhD

Professor

Department of Molecular Pharmacology,
Physiology, and Biotechnology
Brown University
Providence, Rhode Island
March 12, 2007

LTP at GABAergic Synapses in the Reward Pathway

The best characterized cellular mechanisms proposed to underlie information storage in the CNS are long-term potentiation and long-term depression (LTP and LTD). It is well established that excitatory glutamatergic synapses are strengthened or weakened in response to specific patterns of synaptic activation, and considerable evidence has accumulated suggesting that such changes in synaptic strength occur during learning and other adaptive responses to environmental stimuli. A single exposure to a variety of addictive drugs similarly potentiates excitatory synapses on dopaminergic cells in the ventral tegmental area (VTA). We have discovered a novel form of LTP (at GABAergic synapses onto VTA dopamine cells) that is prevented by exposure to opiate drugs.

GABAergic neurons represent up to 35 percent of VTA neurons. They act as local interneurons to inhibit VTA dopaminergic neurons and also provide important projections to the nucleus accumbens and prefrontal cortex. The normal functioning of GABAergic synapses in the ventral tegmental area is also altered as a result of *in vivo* exposure to drugs of abuse; at least two major classes of addictive drugs—opioids and ethanol—exert potent, direct effects on GABAergic synaptic transmission. We therefore investigated long-term potentiation of GABA_A mediated inhibitory synaptic currents (IPSCs), using whole-cell recordings from VTA slices. High-frequency stimulation (100 Hz, 1 second, repeated twice; HFS) induced LTP_{GABA} of IPSCs onto DA cells. This form of LTP is heterosynaptic, requiring an NMDA

receptor-dependent increase in postsynaptic intracellular Ca²⁺ but resulting from increased presynaptic GABA release. Nitric oxide acts as a retrograde messenger linking postsynaptic NMDAR activation in dopamine neurons with increased synaptic release of GABA.

LTP_{GABA} is absent after *in vivo* exposure to morphine, providing a novel mechanism by which μ -opioids trigger a long-lasting modulation of inhibitory circuits in the VTA. Our work suggests that twenty-four hours after a single treatment with morphine, GABAergic synapses in the VTA cannot potentiate in response to nitric oxide, but can potentiate in response to cyclic GMP, a downstream signal. These data suggest that the nitric oxide-sensitive cyclic GMP-producing enzyme, guanylate cyclase, either is downregulated or becomes insensitive to nitric oxide after morphine. This neuroadaptation to opioid drugs may contribute to early stages of addiction and may also be exploited therapeutically by drugs targeting GABA_A receptors or guanylate cyclase.

Supported by DA11289, NS050570, NARSAD and F32 DA 018023.

Mark Bear, PhD

Professor
Department of Brain and
Cognitive Sciences
Director, Picower Institute for
Learning and Memory
Massachusetts Institute of Technology
Howard Hughes Medical Institute
April 23, 2007

Mechanisms for Visual Cortical Plasticity

When we experience something new, some synapses in the brain grow stronger and other synapses grow weaker. Memory is encoded in this pattern of synaptic change. Our lab examines how synaptic transmission is potentiated or depressed as a function of experience; how these processes are regulated to keep the network of synapses within a useful dynamic range; and how the qualities of synaptic plasticity vary across the lifespan. Insights gained in these studies have suggested novel therapies for mental retardation that are now being tested.

We seek to understand how synapses in the cerebral cortex are modified by experience. Key insight into this process has been gained over the past forty years by recording the activity of cortical neurons *in vivo*. These studies show that a cardinal feature of cortical neurons is stimulus-selective receptive fields. For example, neurons in the primary visual cortex show selectivity to particular stimulus attributes, such as which eye is stimulated, or the orientation of a contrast border; neurons in the CA1 region of the hippocampus show selectivity for positions in space, and so on. Selectivity in many cortical areas can be modified by experience; in fact, experience-dependent shifts in selectivity are the most common correlate of memory formation. Lasting shifts in selectivity are believed to reflect synaptic changes that, distributed over a population of cells, are the neural basis of memory storage. Thus, we frame the question

as follows: How do cortical synapses adjust their effectiveness to modify neuronal selectivity and store information?

By combining theoretical analysis with a reductionist experimental approach, we have uncovered properties of synaptic modification that can, in principle, account for observed experience-dependent changes in cellular responses. We established that synapses throughout the cerebral cortex are bidirectionally modifiable, and that the sign or polarity of the modification depends on the type of NMDA receptor (NMDAR) activation at the time of induction. We also showed that the conditions required to induce long-term synaptic potentiation (LTP) or depression (LTD) vary depending on the history of cellular or synaptic activity, a property now called metaplasticity.

The major questions that confront us now are the molecular mechanisms of bidirectional synaptic plasticity and metaplasticity, and—of particular importance—the contributions of these mechanisms to naturally occurring synaptic modifications in the brain. We are employing a wide range of techniques—biochemical, anatomical, electrophysiological, and behavioral—to address these key questions in the hippocampus and visual cortex.

**The M. R. Bauer
Distinguished Lecturer
Series Summaries
2006–2007**

Introduction

Once again, this year's M. R. Bauer Distinguished Guest Lecturer Series Program was outstanding. The program, now completing its eighth year, brought two international leaders in neuroscience to campus: Richard Tsien and Tobias Bonhoeffer. During their weeklong visit, each of our distinguished visitors gave both formal and informal presentations to the Volen Center and visited individual laboratories for valuable one-on-one discussions with our students. This mutual exchange of ideas and data remained a high point of the visits.

Richard Tsien, PhD

Professor
Department of Molecular and
Cellular Physiology
Stanford University
Stanford, California
February 5, 2007

Deciphering Fundamental Units of Neural Communication

Dr. Tsien presented new and unpublished work that provides new insights into signaling at neuronal synapses. One area of research focuses on the existence and functional meaning of multiple modes of synaptic vesicle fusion triggered by Ca^{2+} . The opening of the Ca^{2+} channels drives at least two distinct forms of fusion. In the classical mode, known as "full-collapse fusion," the vesicle membrane fully merges with and flattens into the presynaptic membrane. In a newly characterized mode, termed "kiss-and-run" (K&R), the connection between the vesicle interior and the external medium lasts long enough to allow passage of neurotransmitter, but the connection is severed before the identity of the vesicle is lost. Dr. Tsien studies the dynamic properties and functional implications of both fusion modes by loading single synaptic vesicles with single photoluminescent reporter particles—quantum dots. Sharp distinctions between full-collapse fusion (FCF) and K&R are now in hand. The same vesicle could undergo K&R and then FCF, as soon as the next stimulus, ten seconds later. Rapid imaging of the decay of fluorescence associated with a typical K&R event indicated that the fusion pore was open for well below 1 s and that the reacidification

proceeded rapidly, with a time constant of ~ 1 s. The prevalence of K&R and FCF depends on the stimulus pattern during the processes of Qdot loading and unloading. Imaging of Qdots not only provides a new perspective on intriguing and controversial issues of vesicle dynamics, but also offers the possibility of tracking presynaptic activity within neuronal circuits over extended periods.

Another topic concerns the fundamental unit of cell-cell communication between brain neurons: quantal synaptic transmission. Presynaptic release of a packet of neurotransmitter—for example, glutamate—causes activation of postsynaptic receptors and a brief flow of current that promotes firing of the postsynaptic cell. Dr. Tsien's group works on neuronal mechanisms that allow synapses to adapt to a sudden or long-lasting change in their level of activity. For example, blocking impulses or postsynaptic glutamate receptors causes a cascade of biochemical events that eventually leads to readjustment of critical molecular players on both sides of the synapse. The group uses state-of-the-art methods to pin down the cell biology of changes in synaptic strength in cultures of isolated neurons and brain slices. Their experiments demonstrate that adaptation may take place both post- and presynaptically, with patterns of modification that differ sharply from one kind of synapse to another in hippocampal circuits.

One of the more profound effects of synaptic transmission and cellular depolarization is to cause changes in neuronal gene expression. Despite its importance, signaling from synapse or surface membrane to nucleus is only partly understood. One example of such signaling involves a local increase in Ca^{2+} concentration near class of Ca^{2+} channels (L-type) different from those that trigger presynaptic release, subsequently leading to activation of exemplar transcription factor, CREB, a transcription regulator of many important neuronal genes.

The group's approach is to combine physiological approaches (how fast, how steeply voltage-dependent, how signal is transduced) and biochemical experiments using cDNA microarrays (which genes, in what context, what relationship to learning and memory). Recently, they have shown that excitation-transcription is every bit as steeply voltage-dependent as excitation-dependent as excitation-contraction or excitation-secretion coupling, but shows its own unique biological features.

Tobias Bonhoeffer, PhD

Director
Max Planck Institut fuer Neurobiologie
Muenchen-Martinsried, Germany
May 7, 2007

How Activity Changes Synapses in the Mammalian Brain

One of the most fundamental properties of the brain is its ability to adapt rapidly to environmental changes. This is achieved mainly by changes in the connectivity between individual nerve cells. Synapses can be modulated in their strength by a variety of different mechanisms. We have investigated a number of these mechanisms, ranging from homeostatic control of synaptic efficacy to morphological manifestations of synaptic strengthening or weakening, and the role of calcium in these processes. Yet, while we are beginning to understand the cellular mechanisms underlying synaptic changes, it is important to consider the functional implications of synaptic plasticity in the intact brain. We are therefore applying new imaging methods to investigate the effects of experience on synaptic changes in cortical circuits. In particular, *in vivo* two-photon microscopy has enabled us to study morphological as well as functional plasticity at the level of individual neurons in the neocortex. These experiments are beginning to close the gap between traditional cellular and systems studies, and they will enable us to obtain a much more comprehensive understanding of the phenomenon of synaptic plasticity and its role in cortical function and ultimately behavior.

Brandeis University

The M. R. Bauer Foundation Scientific Retreat 2007

The 2007 Volen National Center for Complex Systems retreat was held at MIT's Endicott House. Five of our newest Brandeis faculty members spoke about a variety of topics. The interdisciplinary nature of this retreat is a fine example of the diverse scientific efforts of the Volen Center. The day was a total success, with excellent speakers; informative posters presented by postdocs and graduate students; and a delicious and relaxed buffet dinner.

Volen National Center for Complex Systems Annual Retreat, 2007

“Expanding Horizons”

Thursday, April 5, 2007
Endicott House
Dedham, Massachusetts

10:00 a.m.
Arrival and Registration

10:30 a.m.
Daniela Nicastro, PhD
“The New Ice Age: Cryo-Electron
Tomography”
Assistant Professor of Biology
Brandeis University

11:15 a.m.
Douglas Theobald, PhD
“Procrustes Meets Theseus:
Maximum Likelihood Superpositions”
Assistant Professor of Biochemistry
Brandeis University

12:00 p.m. Lunch

1:30 p.m.
Michael Hagan, PhD
“Dynamic Pathway for Viral Capsid
Assembly”
Assistant Professor of Physics
Brandeis University

2:15 p.m.
Paul Garrity, PhD
“Feeling the Heat: Thermosensory
Behavior in *Drosophila*”
Associate Professor of Biology
Brandeis University

3:00 p.m. Break

3:30 p.m.
Angela Gutchess, PhD
“Memory Specificity with Age”
Assistant Professor of Psychology
Brandeis University

4:15 p.m. Poster Session

5:15 p.m.
Diane Simonds
“A Brief History of the Endicott House”

5:40 p.m. Buffet Dinner

Daniela Nicastro, PhD

Assistant Professor of Biology
Brandeis University

The New Ice Age: Cryo-Electron Tomography

When studying an organism that is very small, it is important to use an imaging technique that will give the clearest picture of shapes and structure. Two-dimensional images can give snapshots of an area, but they cannot truly represent the structure of a three-dimensional object. Dr. Nicastro's lab uses a technique called cryo-electron tomography to image cells three-dimensionally at a very high resolution.

An electron microscope uses a beam of electrons to image a specimen, instead of the beam of light used by traditional microscopes. The electron beam offers a higher resolution than a light beam would, but because the electrons have to travel through a vacuum the specimen needs to be protected. Dr. Nicastro uses a method of fast freezing that preserves the cell structure more than a dehydration technique would. Tomography is a process of taking a series of two-dimensional images from different angles, and then using the images to reconstruct a three-dimensional view. This 3D image can then be rotated on a monitor, so that organelle structure and placement can be examined from all angles.

Dr. Nicastro showed examples of work that she has done using this technique, including imaging of eukaryotic flagella. Flagella are used by the cell in locomotion, but their function is not yet understood. Tomographic imaging was able to show a structure of microtubules that compose the flagella, as well as the protein dynein that is responsible for the movement of each microtubule. Each microtubule moves in relation to its neighbor, and this is thought to be the process by which speed and propagation of movement in these cells is controlled. This level of detail would not be available using other types of imaging.

Douglas Theobald, PhD

Assistant Professor of Biochemistry
Brandeis University

Procrustes Meets Theseus: Maximum Likelihood Superpositions

The Protein Data Bank is a collection of protein structures that labs can use to compare new structures to ones already identified. This is done by fitting the new structure to old using "superpositioning," a way of fitting the atomic structures as closely as possible. But models are imprecise, and variance can be very high. To interpret whether superpositioning has found the most accurate fit, scientists use a statistical analysis called the least squares method. This method assumes that the best fit is that with the minimum sum of squared differences between the structures—but this method assumes equal variance. Since variance is so high, scientists often just trim off the regions that are unsuperimposable, losing information that could be important.

Dr. Theobald discussed a new method of analyzing the similarity of structures based on the maximum likelihood principle. Maximum likelihood downweights the variable regions instead of trimming them off, which gives a better statistical fit. To use this method, first a statistical model (Gaussian, for example) is chosen to best represent the data. Parameters for the model are set to predict the data with the highest probability, such as the mean structure and a covariance matrix: each atom in the structure has its own variance and it co-varies with other atoms. Maximum likelihood uses the covariance matrix to downweight the variable regions.

Dr. Theobald has written a program, Theseus, which uses maximum likelihood for superpositioning. In a simulation using simulated structures, a comparison between the two statistical methods showed that maximum likelihood to be much more accurate than least-squares, that less information is lost due to variance, and that this method will prove very helpful for use in structural biology.

Michael Hagan, PhD

Assistant Professor of Physics
Brandeis University

Dynamic Pathway for Viral Capsid Assembly

The outer shell of a virus is called a capsid—it is there to surround and protect the genetic material of the virus, and it enables the virus to infect another cell. The capsid attaches to the cell and inserts the genetic material inside, allowing the virus essentially to take over and begin replication. This capsid shell is assembled with a series of protein interactions, the specific processes of which are still unknown. Questions such as what factors in these proteins are necessary for assembly, and whether there is any possibility of external control (such as blocking it from happening) are currently being studied.

Dr. Hagan has created a computational model of capsid assembly that he believes will help answer some of these questions. In his model, he can alter parameters and make the capsid more or less likely to form a complete, working structure. In this way, he can observe the dynamics of the protein interactions individually. The parameters he can play with include binding energy, angle tolerance, concentration, and time; a change in any of these will alter capsid formation. When the parameters are finely tuned, the proteins will interact, binding and unbinding, searching for the optimal connections. As these connections are found, the proteins begin to form a sphere—beginning

with a ring of proteins of which each has two bonds, making it stable. This ring is the basis of the nucleus, and the rest of the capsid forms around it.

When the parameters are changed, the dynamics of the interactions change. More of the less-optimal connections, which would have been broken in the finely tuned model, will stay bound, and the capsid will contain multiple defects. These defects prevent the capsid from forming a closed structure. Therefore, very narrow parameters are needed for the viral capsid shell to assemble properly. Since the virus needs a properly assembled capsid to attach and infect a cell, this model could help to find ways to stop a virus from replicating.

Paul Garrity, PhD

Associate Professor of Biology
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Feeling the Heat: Thermosensory Behavior in *Drosophila*

The ability to recognize changes in temperature is vitally important to survival in most species. The thermosensory system can keep an animal (or human) from exposure to extreme temperatures (such as the jerk reflex when touching a hot stove). It can help an animal find an appropriate environment in which to live. Some animals can even use it to find prey. A snake, for example, has infrared sensors in its facial pit; these sensors can detect a 0.003°C change in temperature, allowing the snake to catch prey even in the dark. A human can sense temperature changes as small as 0.1°C. Thermosensory behavior is even seen in the common fruit fly, *Drosophila melanogaster*. But the genetic and molecular mechanisms behind this behavior are not yet fully understood.

Dr. Garrity's lab uses both the adult and larval fruit fly to study these mechanisms. *D. melanogaster* larvae are quite sensitive to temperature changes, and, when placed on a dish that is cool on one side and warm on the other, they will move toward the cooler side. The Garrity lab has identified a gene, dTRP1a, which is essential for thermotaxis, the recognition of temperature. When this gene is knocked out in larvae, they can no longer make the choice between cool and hot. Dr. Garrity's team found that dTRP1a is needed for thermotaxis in both larvae and adults, but not for high-temperature recoil, a behavior in flies similar to jerking away from a hot stove. Flies lacking in dTRP1a are still able to exhibit recoil behavior, meaning there is a separate neural circuit involved.

Dr. Garrity ended his talk with a discussion of a new comparative study the lab is involved in, comparing *D. melanogaster* with another type of fruit fly, *Drosophila mojavensis*, which lives in the Sonoran desert. These flies live in cacti and can survive temperatures up to 110°F. They are comparing the two dTRP1a genes to see what differences between them can account for the different heat thresholds seen in these two related species.

Angela Gutchess, PhD

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Memory Specificity with Age

That aging affects the memory system is fairly obvious. What isn't as obvious is why, where, or how this effect is taking place. A decrease in short-term memory could be due to a loss of specificity and function, or it could be due to a decrease in attention, or even a general slowing of cognition that naturally happens as the brain ages. By comparing responses of young adults and elderly subjects performing the same experimental task, scientists can draw a clearer picture of how the brain might be changing over time.

In her talk, Dr. Gutchess presented some of her work with functional magnetic resonance imaging, or fMRI, as a way to study the changes in brain function due to aging. In general, there is a loss of specificity in older adults, meaning their cortex responds more generally to a task. For example, in recall tasks, a young brain would usually show only right-hemisphere activation, while an older brain often shows both left and right. Dr. Gutchess discussed an experiment using an adaptation paradigm in which subjects were shown the same image over and over again. Activation decreases in both young and old as the repetitions increased, as they are adapting to the image. When there was a change in the image, different activation patterns occurred in the two subject groups. If the object of the image changed, the young subjects showed an increase of

activity in the right lateral occipital cortex, an area that has been shown to respond to objects. This activation wasn't seen in older subjects, suggesting they weren't distinguishing between old and novel.

Dr. Gutchess discussed other experiments, such as one that examined whether relating a list of adjectives either to the self or another person improves memory for the items on the list. Her work has shown that there are different areas being activated in memory tasks between young and old; loss of specificity was seen in more than one study, possibly indicating that older brains are recruiting more areas to help with tasks.

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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