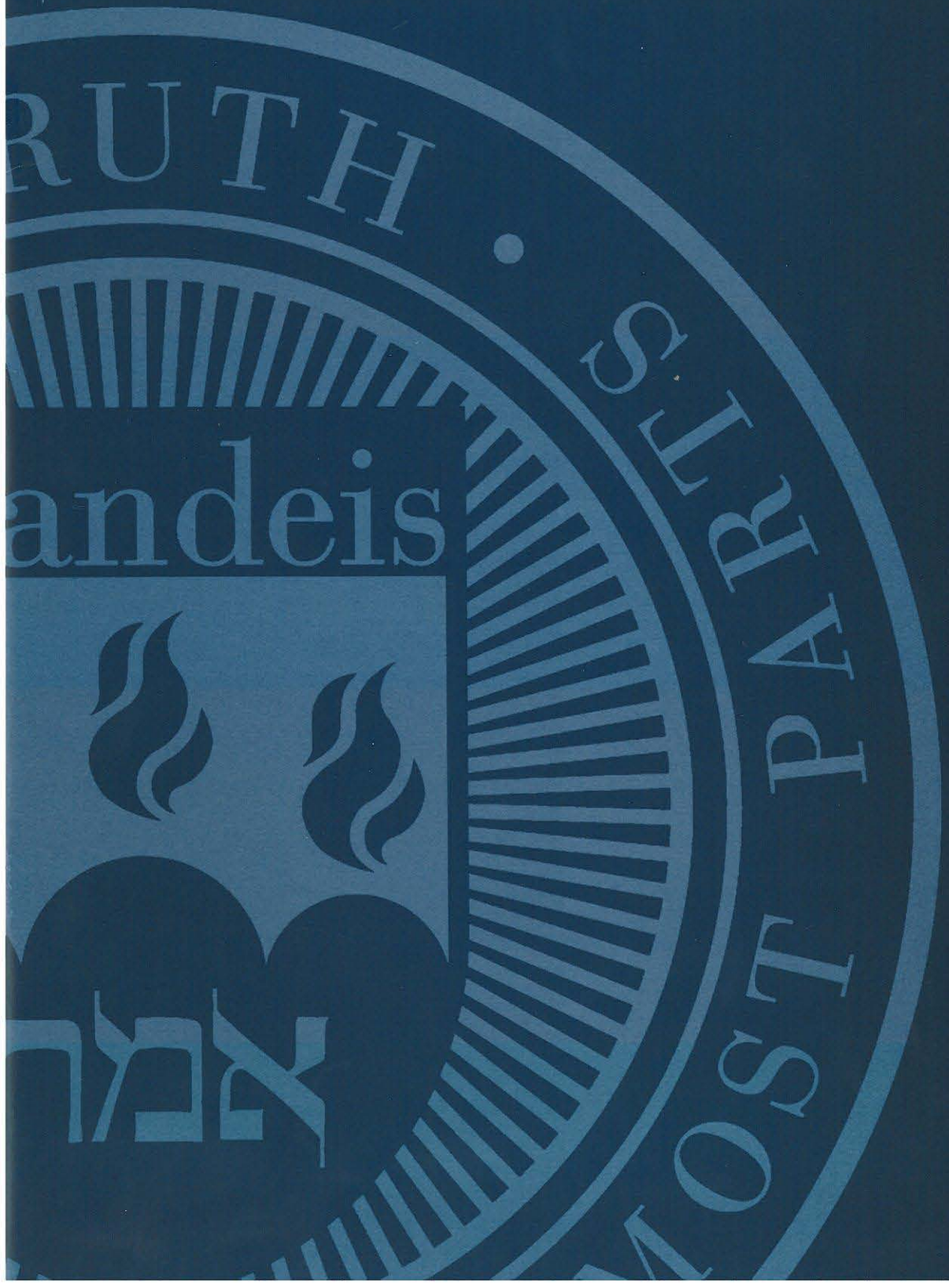
Brandeis University

Benjamin and Mae Volen National Center for Complex Systems

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

August 2006



The M.R. Bauer Foundation Colloquium Series, Distinguished Lecturer Series, and Scientific Retreat 2005–2006 Summary

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Introduction

The 2006 M.R. Bauer Foundation Colloquium Series, Annual Scientific Retreat, and Distinguished Guest Lecturer Series

I am very pleased 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 twelfth year, the generous support of the M.R. Bauer Foundation has enabled the Volen Center to showcase emerging knowledge in the quickly moving field of neuroscience to a broad audience in the scientific community. Indeed, in the past academic year the Volen Center has mounted an impressive series of lectures and informal interactions that reflect innovative research in neuroscience. My colleagues and I would like to express our deep appreciation to the M.R. Bauer Foundation for its abiding support, which has facilitated learning and communication among the faculty and students with many of the most highly regarded practitioners of neuroscience.

The *2005–2006 M.R. Bauer Colloquium Series* again featured talks by some of the most outstanding neuroscientists at universities, medical schools, and research institutes. **Stephen R. Williams**, PhD, from the Neurobiology Division of the Medical Research Council Laboratory of Molecular Biology in Cambridge, United Kingdom, spoke on the topic "Distributed Synaptic Integration in Cortical Pyramidal Neurons." Dr. Williams's research involves single neuron computation and focuses on the ways neurons compute patterns of synaptic input to form a neuronal output. **Robert Desimone**, PhD, from the McGovern Institute of Brain Research at the Massachusetts Institute of Technology, delivered a talk on "Neural Synchrony and Selective Attention." Dr. Desimone's research centers on disorders of perception, attention, and memory that frequently accompany the major mental diseases. To understand the neural mechanisms of these mental processes, his laboratory is recording the activity of neurons in the extrastriate and prefrontal cortex of nonhuman primates engaged in tasks requiring visual discrimination, attention, and memory. **Anne B. Young**, MD, from the Department of Neurology at Massachusetts General Hospital, addressed "Huntington's Disease from Bench to Bedside." Dr. Young's laboratory has focused on two primary areas of research: the functional anatomy of the mammalian basal ganglia; and the role of excitatory amino acids in neurodegenerative diseases such as Alzheimer's disease, Huntington's disease, and Parkinson's disease. **Carol Mason**, PhD, from the Center for Neurobiology and Behavior at Columbia University Medical Center, examined the topic "The Genes, Guidance Factors, and Cells that Pattern the Optic Chiasm." The primary aim of Dr. Mason's research is to understand the mechanisms that underlie axon growth and the formation of specific synaptic connections. Her laboratory uses a battery of static and dynamic microscopic approaches in vivo and in cell culture to dissect the molecular mechanism's development of neural circuits. **Xandra Breakefield**, PhD, from the Department of Neurology at Massachusetts General Hospital, spoke about "Following a Twisted Path: From Dystonia to the Endoplasmic Reticulum." Dr. Breakefield's work is currently focused on the development of vectors for gene delivery to the nervous system; use of virus vectors for experimental therapy of brain tumors; and elucidation of the molecular etiology of torsion dystonia.

Now in its eighth year, the *M.R. Bauer Distinguished Guest Lecturer Series* brought three well-known scientists to campus for extended visits. **Marcus E. Raichle**, MD, PhD, from the Departments of Radiology and Neurology at the Washington University School of Medicine, is a leader in using positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) to study aspects of human brain organization and function in health and disease. His current research focuses on the intrinsic functional activity of the brain as distinct from evoked responses related to behavioral events. In his presentation, "Spontaneous Activity and the Brain's Dark Energy," Dr. Raichle shared evolving ideas in the area of cognitive psychology, describing background

information from an imager's perspective and offering a sense of perspective on the "dark energy" of the brain. The program brought together for the first time a team of scientists whose work has affected the entire field. **Louis Ptacek**, PhD, a Howard Hughes Medical Institute investigator and professor of Neurology at the University of California, San Francisco, School of Medicine, is interested in identifying genes that can cause diseases of the nervous system and studying both the normal and mutant proteins encoded by some of these genes. His goal is to understand normal brain function, including human sleep behavior, and the molecular basis of diseases such as epilepsy and migraine headaches. His presentation, "Channelopathies: Molecular Basis of Episodic Nervous System Disorders," considered episodic nervous system disorders—including epilepsy and periodic paralysis—and analyzed their similarities and precipitating factors. **Ying-Hui Fu**, PhD, also from the Department of Neurology at the University of California, San Francisco, School of Medicine, is interested in understanding the mechanisms of various diseases involving the nervous system. In particular, there are two classes of neurodegenerative diseases that Dr. Fu's laboratory is focusing on: polyglutamine diseases and demyelinating degenerative diseases. Dr. Fu's lab is also researching human circadian rhythmicity, which was the focus of her presentation, "Molecular and Genetic Basis of Human Circadian Rhythmicity." Dr. Fu explained how we can understand human circadian rhythms, considering genetic, social, and familial-cultural influences, and looked closely at the pattern of early morning awakening in aging Advanced Sleep Phase Syndrome (ASPS).

Highlighting "Diseases as Complex Systems," the *2006 Volen Center Scientific Retreat,* sponsored by the M.R. Bauer Foundation, was held at the Shapiro Campus Center at Brandeis University on May 24. The event was attended by some 110 faculty, staff, and students, including visitors from other institutions. This year's retreat featured talks by four university scientists, as well as the previously mentioned presentation by **Xandra Breakefield**, PhD. Each scientist focused on presenting information and leading-edge research about the central nervous system and neurodegenerative diseases that affect it. **Gina Turrigiano**, PhD, professor of Biology, Volen National Center for Complex Systems at Brandeis University, discussed "The Self-Tuning Neuron: Homeostatic Plasticity of Neocortical Synapses." In addition, **Pengyu Hong**, PhD, assistant professor of Computer Science, Volen National Center for Complex Systems, presented a talk on "Mining Biological Data." **Jeff Agar**, PhD, assistant professor of Chemistry, Volen National Center for Complex Systems, spoke about "Cause and Consequence of Protein Aggregation in Familial ALS." The final talk was given by **Jozsef Fiser**, PhD, assistant professor of Psychology, Volen National Center for Complex Systems. His talk was on "The Role of Spontaneous Activity in the Primary Visual Cortex."

Over the past twelve years, the M.R. Bauer Colloquium and Scientific Retreat have promoted the exchange of ideas and methods to advance the study of neuroscience. In the past eight years, the M.R. Bauer Distinguished Guest Lecturer Series has brought highly regarded neuroscientists to the university to speak about their groundbreaking research. The publication of these Bauer proceedings is an essential part of the Volen Center's effort to encourage scientific collaboration and discussions. On behalf of our colleagues and the many participants in these Foundation-sponsored programs, we would like to express our sincere appreciation to the M.R. Bauer Foundation.

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

Stephen R. Williams, PhD
Neurobiology Division
Medical Research Council
Laboratory of Molecular Biology
Cambridge, United Kingdom
September 26, 2005

Distributed Synaptic Integration in Cortical Pyramidal Neurons

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The neocortex is a complex structure, with each neuron receiving thousands of synaptic inputs from other elements of the network. Dr. Williams aims to explore at a mechanistic level: 1) how individual neurons of the neocortical network integrate synaptic input; and 2) how the pattern of action potential output influences forward transmission of information through neocortical networks. To this end he has developed techniques that enable the recording of postsynaptic potentials (PSPs) from sites throughout the apical dendritic arbor of a class of layer 5 neocortical pyramidal neurons.

Dr. Williams and his laboratory found that single excitatory PSPs (EPSPs) generated at sites remotely in the dendritic arbor have relatively little direct influence on action potential output, due to a uniformity of synaptic conductance. In contrast they found that trains of EPSPs, generated from distal dendritic sites, provide powerful drive action potential output through the engagement of active dendritic spiking mechanisms. Interestingly, they found that identical inputs generated from somatic and distal apical dendritic sites generate action potential output patterns that are statistically distinct and that may be broadly classified as simple single action potential firing and action potential burst firing, respectively.

To explore how such output patterns are propagated through the neocortical network, the lab made multineuronal whole-cell recordings. To their surprise they found that the dynamics of synaptic transmission between layer 5 neocortical pyramidal neurons are tuned to allow the reliable signaling of action potential burst discharges, but not single spikes. Dr. Williams concluded that distal excitatory synaptic inputs decisively control the excitatory synaptic output of layer 5 neocortical pyramidal neurons and, therefore, are a powerful influence on network activity in the neocortex.

Robert Desimone, PhD
Director
McGovern Institute
Brain and Cognitive Sciences Department
Massachusetts Institute of Technology
Cambridge, Massachusetts
December 5, 2005

Neural Synchrony and Selective Attention

Dr. Desimone's most recent work has focused on the neural mechanisms that promote or limit the ability to respond selectively to one stimulus seen in a multitude of stimuli. Humans' ability to perform such selective filtering is as limited as it is crucial to normal, everyday function. His lab is attempting to understand the neural substrate of those limitations and, potentially, the source of individual differences in this important ability.

Neural systems for visual processing can focus attention on behaviorally relevant objects, filtering out competing distractors. Neurophysiological studies in animals and brain imaging studies in humans suggest that such filtering depends on top-down inputs to extrastriate visual areas, originating in structures important for attentional control. In order to carry out his research program, Dr. Desimone's laboratory uses a variety of techniques, including recordings from single and multiple neurons in various regions of the primate brain, analysis of high-frequency (gamma band) activity and synchronization in the primate brain, and sophisticated behavioral paradigms, particularly ones designed to assess visual spatial attention.

To optimize the limited capacity for selective filtering of incoming inputs, he suggested that the brain's attentional mechanisms must give priority to behaviorally relevant stimuli—usually at the expense of irrelevant stimuli. He has demonstrated that in several visual areas of the primate brain, attended stimuli induce enhanced responses and an enhanced synchronization of rhythmic neuronal activity in the gamma frequency band (40–70 Hz). Both of these effects are likely to improve the signal-to-noise ratio associated with attended stimuli, both within any one brain region and among different brain regions.

Attention also results in improved behavioral performance, as assessed by accuracy and shortened reaction times. Although that result has been replicated many times over the years, it was not known how reaction times were related to either response strength or gamma-band synchronization in visual areas. Dr. Desimone showed that behavioral response times to a change in stimulus can be predicted by the degree of gamma-band synchronization among those neurons in monkey visual area V4 that are activated by the behaviorally relevant stimulus. When there are two visual stimuli and monkeys have to detect a change in one stimulus while ignoring the other, their reactions are fastest when the relevant stimulus induces strong gamma-band synchronization before and after the change in stimulus. This enhanced gamma-band synchronization is also followed by shorter neuronal response latencies on the fast trials. Conversely, the monkeys' reactions are slowest when gamma-band synchronization is high in response to the irrelevant distractor. Thus, enhanced neuronal gamma-band synchronization and shortened neuronal response latencies to an attended stimulus seem to have direct effects on visually triggered behavior, reflecting a very early neuronal correlate of efficient visuomotor integration.

Anne B. Young, PhD
Professor
Department of Neurology
Massachusetts General Hospital
Boston, Massachusetts
January 30, 2006

Huntington's Disease from Bench to Bedside

Huntington's disease (HD) is an autosomal dominant inherited disorder that affects approximately four to ten out of each 100,000 members of the population. It begins insidiously in midlife with personality changes and involuntary jerk-like movements of the limbs, chorea. The illness results in inevitable death after about fifteen years of illness. The mutation in the HD gene that causes the illness is an unstable, expanded trinucleotide (CAG) repeat in the N-terminal region of the open reading frame.

In the last five years, numerous studies have been carried out examining the potential mechanisms whereby the gene may cause the pathology. It is now possible to examine these mechanisms in cell-based assays and whole animals (including drosophila and c. elegans). Dr. Young and her laboratory devised a set of strategies to look for compounds that delay the onset and slow the progression of the disease. They chose to use assays that examine the most fundamental aspects of protein mishandling. She has also set up a laboratory for high throughput screening of compound libraries to assess methods to improve function in cell-based assays and animal models.

To date, they have found one compound, C2-8, that reduces inclusion formation and aggregation and slightly improves survival in HD transgenic mice. They have also found compounds that increase aggregation but improve survival in cell-based assays. The results suggest that aggregation per se is not toxic, but that other mechanisms involved in the aggregation events may be important. In summary, drug discovery in academia is possible and will hopefully interface with biotechnology and pharmacological goals.

Carol Mason, PhD
Professor
Center for Neurobiology and Behavior
Columbia University Medical Center
New York, New York
April 3, 2006

The Genes, Guidance Factors, and Cells that Pattern the Optic Chiasm

Light stimuli perceived in the retina are transmitted to relay neurons, the retinal ganglion cells. In mammals, axons of these cells exit from both eyes and converge at the midline of the ventral diencephalon to form the optic chiasm, then project to visual centers in the thalamus and superior colliculus and, from there, to the cerebral cortex. Unlike non-mammalian vertebrates, which have retinal projections to the contralateral side of the brain, in animals with more frontally located eyes some axons do not cross the midline and instead project to the ipsilateral visual centers. This partial decussation allows input from temporal axons of the ipsilateral eye and nasal axons of the contralateral eye, which perceive the same visual hemifield, to converge at higher visual centers, thereby supporting binocular vision and depth perception. In mice, Dr. Mason's model animal, only about 3 percent of RGC axons project ipsilaterally, whereas in humans, nearly 50 percent of axons project ipsilaterally.

Dr. Mason's lecture reviewed her laboratory's analyses over the last two decades designed to study how the optic chiasm is established. They focused on the growing tips of the axons of retinal ganglion cells and chronicled the behaviors of growth cones as they cross, or avoid, the optic chiasm midline to form the binocular projections, a process that occurs in the third gestational week in the mouse. They also characterized the cellular ensembles at the optic chiasm midline. Dr. Mason hypothesized that these specialized glia and neurons express regulatory genes and guidance factors that cordon axons into tracts, specify where the X-shaped chiasm should form, and direct passage of retinal axons across or away from the midline.

More recently, she has identified programs of gene expression and guidance receptor expression for the uncrossed retinal projection. EphB1 receptor is expressed exclusively in the ventrotemporal retinal ganglion cells (RGCs) and is important for interacting with the ligand ephrin-B2 in the midline glia, to cause repulsion away from the midline. The transcription factor Zic2 is expressed similarly in the retina and, like EphB1, is essential for the formation of the uncrossed program. Dr. Mason was able to determine that Nr-CAM, a member of the L1 family of cell adhesion molecules, is required for the act of crossing the midline, especially for a late-born population of retinal ganglion cells from ventrotemporal retina. Such definition of molecular expression in sectors of the retina assigns cell identity and fate with regard to laterality of projection. The study of the retina-optic chiasm pathway not only informs on how the binocular pathways are established, but helps to categorize programs of gene expression for formation of circuits, a current major effort in neuroscience.

New work in Dr. Mason's laboratory seeks to identify: 1) whether the transcriptional regulators that were identified, such as Zic2, directly regulate the expression of guidance receptors such as EphB1; 2) whether the protein for such receptors is locally translated as growth {±nes enter the midline and interact with ephrin-B2-laden radial glia; and 3) the signaling pathways during receptor-ligand interactions.

An offshoot of this work pertains to the human condition, in the genetic model of the albino mammal. Many genes can cause albinism, most of which are important for melanin synthesis or melanin granule packaging turnover. For as yet unknown reasons, the reduction in pigment in cells behind the retina always leads to a dimunition in the uncrossed axonal projection, with resultant problems in binocular vision, photophobia, and misaligned eyes. Because the gene they identified as crucial for the uncrossed component, Zic2, is also reduced, they will be able to make inroads into the connection between perturbations in melanogenesis and perturbed visual pathways.

The M.R. Bauer Distinguished Lecturer Series Summaries 2005–2006

Introduction

Once again, this year's M.R. Bauer Distinguished Guest Lecturer Series Program was outstanding. The program, now completing its eighth year, brought Professors Marcus Raichle, Louis Ptacek, and Ying-Hui Fu to campus. All three are world-class neuroscientists, and their presence on campus during these weeks significantly enriched our life science community.

When on campus, each of these visitors gave a public seminar, spoke at the neurobiology journal club, met with postdocs and graduate students, and spent time in many of our neuroscience laboratories getting to know the students and providing invaluable advice to these younger scientists. These weeks are very busy, informative, and enjoyable for all.

Marcus E. Raichle, MD, PhD
Professor
Departments of Radiology and Neurology
Washington University School of Medicine
St. Louis, Missouri

Intrinsic Activity and the Brain's Dark Energy

In the adult human the brain represents about 2 percent of the body weight yet accounts for about 20 percent of its energy consumption, ten times that predicted by its weight alone. A critical question is: What fraction of this large energy budget is directly related to its functions? The answer is, the majority. Depending on the approach used, it is estimated that 60 percent–80 percent of the energy budget of the brain is devoted to its functional activity. This occurs in the form of ongoing events associated with the input and output of neurons, large and small, and the activity in astrocytes in direct support of these processes.

How does this overall cost of brain functions compare to the cost of changes in brain functions elicited by responses to controlled stimuli? Brain-imaging data provide useful, quantitative measures of the cost of changes in brain activity. But it should be noted that inferences derived from the analysis apply broadly across all levels of neuroscience when changes in activity to controlled stimuli are studied.

Brain-imaging signals, whether produced from PET or fMRI, arise from a change in local blood flow that accompanies changes in the local cellular activity of the brain. While PET measures changes in blood flow directly, fMRI senses the changes in local blood oxygen content that arise because blood flow alters more than local oxygen consumption. Thus, the fMRI signal is known as the blood oxygen-level dependent, or BOLD, signal.

The regional increases in absolute blood flow associated with imaging signals as measured with PET are rarely more than 5 percent–10 percent of the resting blood flow of the brain. However, the actual increase in energy consumption associated with these circulatory changes may be as little as 0.5 percent–1.0 percent. These are modest modulations in ongoing circulatory activity that rarely affect the overall rate of brain blood flow during even the most arousing perceptual and vigorous motor activity. From this analysis it becomes clear, then, that the brain continuously expends a considerable amount of energy for functions even in the absence of a particular task (i.e., when a subject is awake and at rest).

From this cost-based analysis of the brain's functional activity it seems reasonable to conclude that intrinsic activity may be as significant, if not more so, than evoked activity in terms of overall brain function. Taking this position converts one's view of the brain from a system primarily responding to external inputs (the traditional view motivating most neuroscience research) to one operating on its own, intrinsically, with sensory information interacting with rather than determining the operation of the system.

Historically, this view has received support from many quarters. It was William James who, in 1890, presciently suggested to the readers of his *Principles of Psychology* that "enough has now been said to prove the general law of perception, which is this, that whilst part of what we perceive comes through our senses from the object before us, another part (and it may be the larger part) always comes (in Lazarus's phrase) out of our own head." In his book *I of the Vortex: From Neurons to Self*, Rodolfo Llinas more recently summarized the evidence for this point of view, beginning with the work of early twentieth-century physiologists through his own contemporary contributions. He concluded that "... the significance of incoming sensory information depends on the pre-existing disposition of the brain, [which] is a far deeper issue than one gathers at first glance ... ."

Louis Ptacek, PhD
Professor
Department of Neurology
University of California, San Francisco
School of Medicine
San Francisco, California

Channelopathies: Molecular Basis of Episodic Nervous System Disorders

Dr. Ptacek's work has focused on studying clinical phenotypes in families to map and clone the genes responsible for various diseases. One focus of such work is episodic neurological diseases. This interest grew out of the mapping and cloning of a number of genes causing periodic paralysis and non-dystrophic myotonia, symptoms that we proposed as a model for other electrical disorders such as cardiac dysrhythmias, epilepsy, and migraine headaches. The genes that he cloned all encode ion channels that are responsible for regulating selective permeability of muscle membranes to various ions. This group of disorders was termed "channelopathies" and has come to encompass not only these muscle diseases but also cardiac arrhythmias, epilepsy, and some migraine phenotypes. Dr. Ptacek's lab has gone on to study the protein products encoded by these genes using cellular electrophysiology. These experiments are useful in proving functional consequences of disease-causing mutations and to a general understanding of the relationship of these channels. Efforts in this group of disorders are expanding into disorders of the central nervous system, including epilepsy and migraine headache.

Ying-Hui Fu, PhD
Associate Professor
Department of Neurology
University of California, San Francisco
School of Medicine
San Francisco, California

Molecular and Genetic Basis of Human Circadian Rhythmicity

Circadian rhythms are one of the best models for studying human behavior. When scientists say "Genetics is everything," it may not be so far-fetched if science comes to recognize just how many human behaviors are influenced by genetic composition. Many physiological processes—including heartbeat, blood pressure, body temperature, and endocrine functions—are subject to circadian regulation. However, the regulation of the overall behavior of an organism is the most overt and intriguing manifestation of circadian rhythmicity. The pursuit of the genetic and molecular basis of behavior is extremely complex because of the wide variation in "normal" individuals. Furthermore, behaviors such as sleep are confounded by social and familio-cultural influences that frequently cause the biological clock to override, leading people to stay up later or wake up earlier than they normally would. Various agents such as caffeine and alcohol also confound one's ability to understand the inherent rhythms dictating human activity. Dr. Fu's lab has identified several mutations that are involved in regulation of human rhythmicity. Molecular studies of in vitro systems as well as in model organisms with human mutations have suggested that the clock is a complicated mechanism, but that it can be approached using molecular and genetic tools.

Brandeis University

The M.R Bauer Foundation Scientific Retreat 2006

The 2006 Volen National Center for Complex Systems retreat was held at Brandeis University's new Shapiro Campus Center. Our keynote speaker, Xandra Breakefield, and four Brandeis faculty members addressed a variety of topics. The interdisciplinary nature of this retreat is a fine example of the scientific efforts and collaborations of the Volen Center. The day was a complete success, with excellent speakers, informative posters presented by postdocs and graduate students, and ended with great food and colleagues enjoying a barbecue on the lawn of the Shapiro Center.

Volen National Center for Complex Systems Annual Retreat, 2006

"Diseases as Complex Systems"

May 24, 2006
Brandeis University
Shapiro Campus Center
Waltham, Massachusetts

11:25 a.m.
Welcoming Remarks
Arthur Wingfield, DPhil
Nancy Lurie Marks Professor of Neuroscience and director, Volen National Center for Complex Systems

11:30 a.m.
Gina Turrigiano, PhD
"The Self-Tuning Neuron: Homeostatic Plasticity of Neocortical Synapses"
Professor of Biology
Volen National Center for Complex Systems
Brandeis University

12:15 p.m. Lunch

1:15 p.m.
Pengyu Hong, PhD
"Mining Biological Data"
Assistant Professor of Computer Science
Volen National Center for Complex Systems
Brandeis University

2:00 p.m.
Xandra Breakefield, PhD
"Following a Twisted Path: From Dystonia to the Endoplasmic Reticulum"
Professor of Neurology
Massachusetts General Hospital
Boston, Massachusetts

3:00 p.m. Break and Poster Session

3:30 p.m.
Jeff Agar, PhD
"Cause and Consequence of Protein Aggregation in Familial ALS"
Assistant Professor of Chemistry
Volen National Center for Complex Systems
Brandeis University

4:15 p.m.
Jozsef Fiser, PhD
"The Role of Spontaneous Activity in the Primary Visual Cortex"
Assistant Professor of Psychology
Volen National Center for Complex Systems
Brandeis University

5:00 p.m. Barbecue

Gina Turrigiano, PhD
Professor of Biology
Volen National Center for Complex Systems
Brandeis University

The Self-Tuning Neuron: Homeostatic Plasticity of Neocortical Synapses

Many developing circuits require experience, in the form of ongoing patterned activity, to become fully functional. Identifying the cellular plasticity mechanisms that underlie this refinement is critical for understanding the role of early experience in normal and abnormal development. Until recently the field had largely concentrated on the role of rapid, synapse-specific forms of synaptic plasticity such as long-term potentiation (LTP) and depression (LTD). However, theoretical considerations suggest that such "Hebbian" forms of plasticity are highly unstable and cannot function efficiently without complementary forms of plasticity that stabilize neuronal and network firing properties. Over the past decade a body of work has identified synaptic scaling, a form of homeostatic synaptic plasticity, as a critical mechanism that provides stability to developing neurons and circuits. This form of plasticity scales neuronal synaptic strengths up or down in the right direction to stabilize firing and appears to operate on the entire distribution of a neuron's synaptic weights. In addition to stabilizing Hebbian plasticity, synaptic scaling likely plays an important role in balancing excitation and inhibition within highly recurrent cortical microcircuits.

Dr. Turrigiano began by discussing the expression mechanism(s) of synaptic scaling at excitatory synapses, with a focus on the role of postsynaptic changes in glutamate receptor accumulation. She contrasted the molecular expression mechanisms of synaptic scaling with those underlying LTP and suggested that there are several pathways for regulating receptor accumulation that operate over different temporal and spatial scales. She then turned to a discussion of the induction mechanism and the role of presynaptic vs. postsynaptic firing in generating a signal for synaptic scaling. Her data suggest that synaptic scaling is a function of postsynaptic firing and is a mechanism that allows neurons to sense their own activity and adjust synaptic strengths to keep this activity relatively constant.

Pengyu Hong, PhD
Assistant Professor of Computer Science
Volen National Center for Complex Systems
Brandeis University

Mining Biological Data

The Computational Systems Biology Lab is interested in developing statistical machine learning techniques and multimedia/multimodal human/computer interfaces to advance biological and biomedical research. One of Dr. Hong's main research activities is the development of new computational methods for dissecting signal transduction networks by integrating heterogeneous biological data—for example, cellular images, transcriptional profiles, bioliterature, and so on. He is also aware of the fact that the quality of computational results can be far from ideal and require nontrivial manual examination. However, biologists often feel overwhelmed by the huge amount, and the great diversity, of biological information. Therefore, Dr. Hong's laboratory is developing novel human/computer interfaces to help biologists effectively and efficiently navigate through the complicated landscape of biomedical information and manipulate various computational tools.

In his talk, Dr. Hong demonstrated his lab's recent progress on a visual data exploration interface for large cellular image databases and a technique for bioliterature categorization. First, using image-processing techniques his lab developed, they extract quantitative information from high-content screening images that are rich in cellular phenotypic information. The extracted information is analyzed by unsupervised pattern-discovering methods. The results can then be visualized in their visual data exploration interfaces. This allows biologists to be directly involved in the data-mining process—combining the flexibility, creativity, and general knowledge of the human race with the enormous storage capacity and the computational power of computers. This process is especially useful when little is known about the data and the exploration goals are vague. Second, they applied Bayesian networks to automatically associate PubMed abstracts with Gene Ontology terms so that the annotated abstracts can be searched semantically. This research is particularly useful for interpreting data generated by high-throughput technologies such as the DNA microarray.

Xandra Breakefield, PhD
Professor of Neurology
Massachusetts General Hospital
Boston, Massachusetts

Following a Twisted Path: From Dystonia to the Endoplasmic Reticulum

Early-onset torsion dystonia (DYT1) is a dominantly inherited movement disorder with affected individuals developing sustained, involuntary muscle contractions and abnormal, twisted posturing. Symptoms result from abnormal functioning of the basal ganglia, but with no apparent neuronal degeneration. Patients are otherwise medically normal with normal-to-high intelligence. Almost all cases of early-onset torsion dystonia are caused by the same mutation, a GAG deletion in the 3' coding region of the message, resulting in deletion of a glutamic acid near the C terminal. The high frequency of this mutation in the Ashkenazic Jewish population is due to a pogrom in Lithuania 350 years ago (a cruel twist of fate).

The novel protein responsible for the disease, torsinA is a member of a family of proteins called AAA—ATPases associated with a variety of cellular activities. AAA-family proteins are the sumo wrestlers of proteins, because they pull or twist protein interactions apart. TorsinA is expressed in all cells, with high levels in neurons in certain regions of the brain. Within cells it is localized predominantly in the lumen of the endoplasmic reticulum—a processing center for membrane-secreted proteins that twists its way around the nucleus and throughout the cytoplasm. TorsinA is involved in connecting the nuclear envelope and endoplasmic reticulum with the cytoskeletal network. The loss of torsinA or its mutant form contort the integrity of the nuclear envelope and the dynamics of the endoplasmic reticulum (neurite extension and synaptic integrity).

Jeff Agar, PhD
Assistant Professor of Chemistry
Volen National Center for Complex Systems
Brandeis University

Cause and Consequence of Protein Aggregation in Familial ALS

Protein post-translational modification underlies most biological processes. The dysregulation of protein modification plays a causative role in a number of disease states, especially the neurodegenerative diseases. Dr. Agar's laboratory studies protein modifications that occur during neurodegeneration and tries to understand the role of these modifications in disease progression. Dr. Agar is also studying the role of protein modification in the process of memory, which can involve modifications as subtle as conformational change. His laboratory uses high-resolution, Fourier transform mass spectrometry (FTMS).

Dr. Agar's talk focused on Amyotrophic Lateral Sclerosis (ALS), which is a late-onset neurodegenerative disease that can be caused by mutations in the gene encoding Cu-Zn superoxide dismutase (SOD-1). The oxidation of tryptophan 32 is found to be present in both as-isolated WT SOD-1 and familial ALS causing G93A SOD-1 using mass spectrometry. In his research, Dr. Agar uses mass spectrometry to determine if there was an effect when mutated tryptophan 32 is used, which forms a residue with a slower rate of oxidative modification, called phenylalanine. When this experiment is done, it is shown to:
1) decrease the cytotoxicity of the G93A mutation to that of WT SOD-1 in a cell culture model;
2) decrease the propensity of mutant SOD-1 to form cytoplasmic aggregates; and
3) increase proteasome activity.

Preventing tryptophan 32 oxidation is therefore a potential strategy for therapeutic intervention in familial, and potentially sporadic, ALS.

Jozsef Fiser, PhD
Assistant Professor of Psychology
Volen National Center for Complex Systems
Brandeis University

The Role of Spontaneous Activity in the Primary Visual Cortex

According to the traditional view, the main role of neurons in the primary visual cortex is to provide a faithful representation of contrast-defined structures in the visual environment for the rest of the cortical visual system through their firing pattern. This firing pattern is contaminated by noise due to spontaneous activity of the cells, but such noise can be overcome by averaging across cells. Such a view is in sharp contrast with the important role attributed to spontaneous activity before eye opening, when correlated ongoing activity is thought to be instrumental in developing functional links and structures in the visual system. How can spontaneous activity change from necessity to nuisance at the moment of eye opening?

To gain insight into this puzzle, Dr. Fiser recorded from the primary visual cortex of awake ferrets at different ages before and after eye opening. Before eye opening he recorded spontaneous activity in complete darkness while the animal was resting. For the age groups with eyes opened, he added two more interleaved visually driven conditions: random noise stimuli and natural scene movies. Dr. Fiser found, first, that spontaneous activity was not random at any age group but instead showed a well-defined spatio-temporal structure that developed according to a clear pattern across age groups from slow irregular bursting to fast, correlated, oscillatory patterns. Second, the temporal and spatial correlational structure of the neural activity was only slightly modulated by the incoming visual stimulation and was constrained to a much larger extent by the internal spontaneous activity. These results suggest a very different view of activity in the primary visual cortex of adult behaving animals. Namely, spontaneous activity is not noise, but rather is generated by the cortical and subcortical systems and represents the internal status of the visual system, reflecting the perceptual state of the animal. Moreover, the incoming visual signal is not coded faithfully in the primary visual cortex, but rather this signal dynamically modulates the evoked internal states represented there by the ongoing activity.

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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