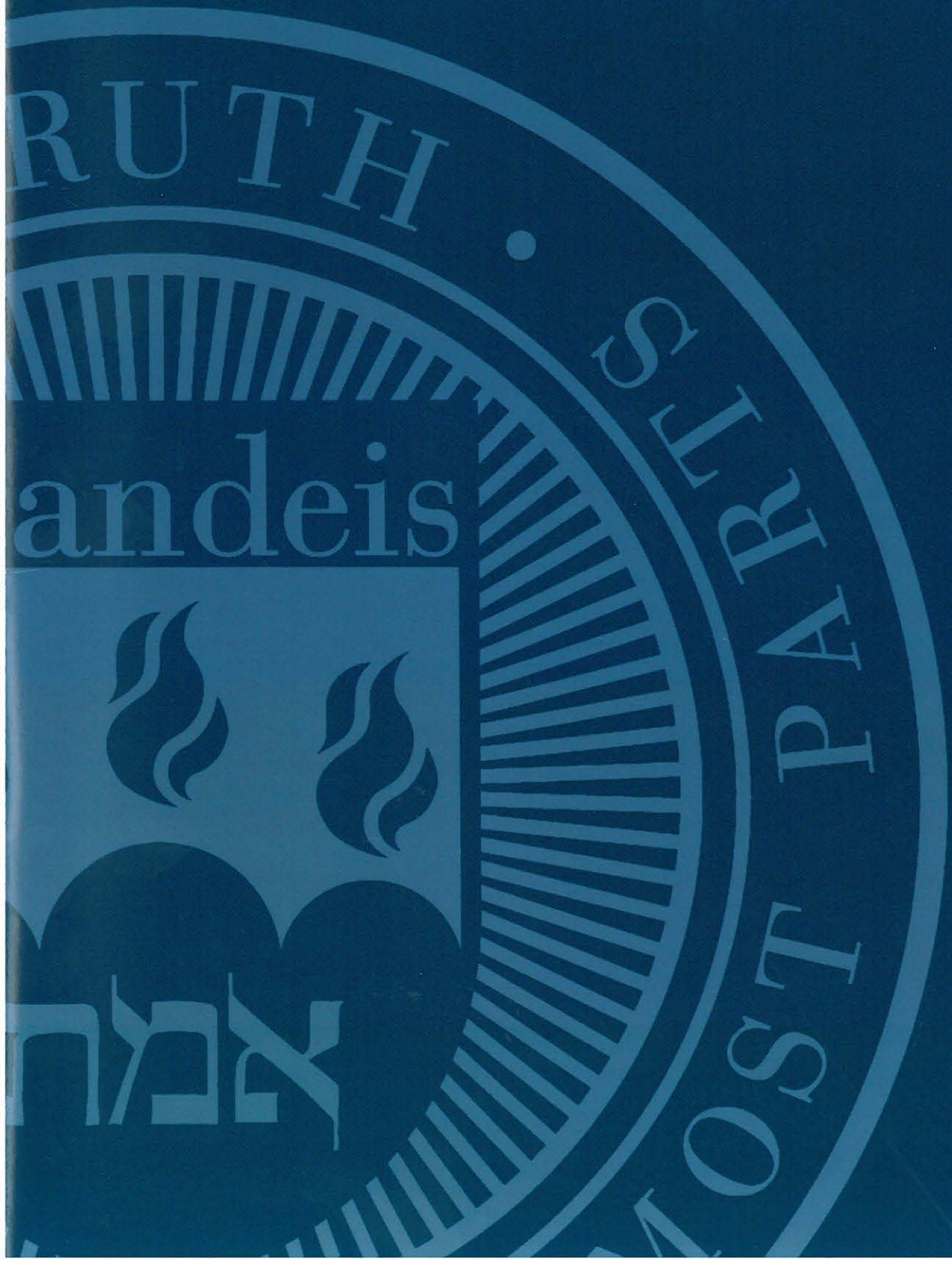
Brandeis University

Benjamin and Mae Volen National
Center for Complex Systems

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

August 2009



The M. R. Bauer Foundation Colloquium Series, Distinguished Lecturer Series, and Scientific Retreat 2008–2009 Summary

Brandeis University

Benjamin and Mae Volen National Center for Complex Systems

Table of Contents

The 2009 M. R. Bauer Foundation Colloquium Series, Annual Scientific Retreat, and Distinguished Guest Lecturer Series

Introduction

Intellectual exchange is the lifeblood of the scientific community, and for fifteen years, the M. R. Bauer Foundation has helped to make the Volen National Center for Complex Systems a center of such exchange in the field of neuroscience. The foundation generously supports three programs—the M. R. Bauer Colloquium Series, the Distinguished Guest Lecturer Series, and the Scientific Retreat—that provide vital opportunities for lively discussion of current research. The Bauer Foundation has been a true partner to the Volen Center, and we remain deeply grateful for this steady, strong support.

The 2008–09 M. R. Bauer Colloquium Series brought to campus four eminent neuroscientists. **Marla B. Feller**, associate professor in the Department of Molecular and Cell Biology at the University of California, Berkeley, spoke on "The Development of Functional Retinal Circuits." Her research starts from the hypothesis that the spontaneous activity patterns of immature neural circuits serve as "test patterns" for the development of the adult nervous system. Focusing on the generation of retinal waves—propagating bursts of action potentials—in the immature mouse retina, she addressed two critical questions: the nature of the underlying cellular mechanisms and the role of retinal waves in the development of retinal circuits. **Anirvan Ghosh**, professor in the neurobiology section of the Biology Division at the University of California, San Diego spoke about "The Dynamics and Regulation of Synapse Formation," describing his lab's work on the molecular mechanisms underlying the development of neural circuits. Dr. Ghosh's research group hopes to develop a model that could aid our understanding of the loss of synaptic connections associated with Alzheimer's disease. **David Anderson**, professor in the Division of Biology, California Institute of Technology, spoke on "Neural Circuits for Innate Defensive Behavior in Mice." His work makes use of genetic, imaging, and behavioral tools to understand fear conditioning, a fundamental behavioral feature that cuts across both human and animal experience. Included in his presentation was a description of his recent work using an insect model to understand the neural circuits that underlie unlearned behaviors. Finally, **Robert H. Brown Jr.**, director of the Day Laboratory for Neuromuscular Research at the Massachusetts General Hospital, presented "Amyotrophic Lateral Sclerosis: Lessons from Genetics." Professor Brown described his laboratory's work using animal models to understand neuromuscular disorders, such as amyotrophic lateral sclerosis (ALS, also known as Lou Gehrig's disease).

The M. R. Bauer Distinguished Guest Lecturer Series was pleased to host a weeklong visit by **Carol A. Barnes.** Dr. Barnes is Regents' Professor of Psychology and Neurology at the University of Arizona, where she also serves as director of the Evelyn F. McKnight Brain Institute. In addition to participating in seminars and meeting with faculty and students, Dr. Barnes presented a lecture titled "Brain and Behavioral Aging: Molecules, Maps, and Memory." Dr. Barnes pointed to evidence of selective anatomical and electrophysiological changes in hippocampal cells in aging humans, monkeys, and rodents. She also explored the effects of these changes on synaptic plasticity. Although quite distinct from the patterns found in Alzheimer's disease, these changes associated with normal aging have consequences for both memory and learning. As we will indicate later in this report, our second Distinguished Guest Lecturer, Professor **Lorna Role**, State University of New York, Stony Brook, faced an unavoidable scheduling conflict and postponed her visit until September. We will summarize her presentation and activities during her visit in next year's report.

The theme of this year's speaker series, as well as the M. R. Bauer Scientific Retreat, was "Connections: The Molecular and Behavioral Neuroscience of Circuit Connectivity." Our keynote speaker at this year's retreat was Dr. Leslie Kay, director of the Institute for Mind and Biology at the University of Chicago. Using a rodent model, Dr. Kay examined how sensations directly produced by external stimuli are transformed into organized percepts. In the olfactory system, this is not a hierarchical process of increasing complexity, but rather a dynamical one in which the pathways between the olfactory bulb (the brain area receiving input from the nose) and other brain areas are fully interactive, and in which the specific mode of processing is affected by the cognitive structure of the task.

Three Volen Center faculty members and a postdoctoral fellow also presented their work at the Scientific Retreat. Two presentations looked at pheromones, a type of chemical cue used primarily for intraspecies communication. **Piali Sengupta**,

professor of neurobiology and the Volen Center, spoke on "Pheromone Signaling in *C. Elegans*." Dr. Sengupta's lab has been investigating the dauer pheromone secreted by the soil nematode *C. elegans*. This research sets the stage for further exploration of these chemical cues in *C. elegans* and other animals.

Aki Ejima, a postdoctoral fellow working in the laboratory of Professor Leslie Griffith, presented her work "Courtship Decision Making Is Regulated by Signal Comparisons between Two Olfactory Pheromone Pathways in *Drosophila melanogaster*." Dr. Ejima's research looks at both the pheromones emitted by female fruit flies to attract males, and the inhibitory pheromones by which males discourage other males. Focusing on the processing of pheromonal information by odorant receptor neurons, Dr. Ejima has found that behavioral output is determined by signal equilibrium between the two olfactory pheromone pathways. Dr. Ejima has recently taken up a faculty position at Kyoto University in Japan.

Paul Miller, assistant professor of biology and the Volen Center, presented "Say That Again: How Auditory Recall Depends on Verbal Stimulus Quality." Working collaboratively with the Wingfield laboratory in the Volen Center, Dr. Miller has explored the intriguing phenomenon that hearing impairment affects recall of speech content, even when the words are recognized correctly. Dr. Miller presented a computational model of word recognition and its effects on the temporal associations that promote recall of adjacent words. Dr. Miller showed how the strength and speed of word recognition can affect the strength of network connections needed for subsequent recall.

Robert Sekuler, professor of psychology and the Volen Center, spoke about "Human Imitation Learning: Mechanisms, Strategies, and EEG." Fidelity of imitation of complex behavior diminishes over the course of the behavior, as measured by algorithms pioneered in Dr. Sekuler's lab. Using tools such as EEG brain wave recordings, his lab's research shows how visual encoding may compete with memory for attentional resources. This points the way toward techniques for facilitating imitative learning, including treatment of neurological conditions that impair imitation.

We have added a brief introduction in italics before each of the more technical presentation summaries. Our goal in adding these short introductions is to place the presentations in their broader context; to "paint a picture" of the connections that exist among these converging approaches to our understanding of brain and behavior, from more molecular approaches to cognition. It is in this spirit that we have adopted "connections" as the theme of this year's M. R. Bauer Colloquia, Distinguished Guest Lecturer series, and annual Scientific Retreat. I hope you will come away not only with new insights into neurological phenomena, but also with an appreciation of the vibrant intellectual life of the Volen National Center for Complex Systems at Brandeis University. This steady, lively exchange of ideas would not be possible without the generous support of the M. R. Bauer Foundation. We are grateful and honored by this long-standing partnership.

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

The M. R. Bauer Colloquium Series Summaries

Introduction

Johann Wolfgang von Goethe, a German writer from the late eighteenth century, has been quoted as saying, "In nature we never see anything isolated, but everything in connection with something else which is before it, beside it, under it, and over it." Although von Goethe was not involved in a scientific discipline, his words embody the true nature of the scientific process. As science progresses, it becomes increasingly clear that complex phenomena are not isolated events, but rather are connected to everything else in nature. Thus, it is not only the connections between neurons and the interactions between genes that underlie biological processes, but also the connections between disciplines, the interactions between people, and the collaborations between institutions that drive science forward. The M. R. Bauer colloquium series provides a rich forum for continued connections to be established at Brandeis University.

Marla B. Feller, PhD
Associate Professor
Department of Molecular and Cell Biology and
Helen Will Neuroscience Institute
University of California, Berkeley
September 8, 2008

The Development of Functional Retinal Circuits

In giving the summaries of our M. R. Bauer Foundation Colloquium Series, we have arranged them not in the order in which the lectures were given. Rather, we felt it more illuminating to arrange them with respect to the "chronology" of organismal development. With these brief introductions, and the more technical summaries that follow, we tell a story that begins with embryonic and early infant development and culminates with adulthood, old age, and in some cases, neurodegeneration.

We begin with the presentation by Dr. Marla Feller, of the University of California, Berkeley, whose research has contributed in important ways to our understanding of how neuronal activity coordinates functional development in the retinal system of the eye.

The Feller lab is interested in the mechanisms underlying spontaneous activity in the developing nervous system and the role this activity plays in the construction of neuronal circuits. There are several examples throughout the developing vertebrate nervous system, including the retina, spinal cord, hippocampus, and neocortex, where immature neural circuits generate activity patterns that are distinct from the functioning adult circuitry. It has been proposed that these transitional circuits provide the "test patterns" necessary for normal development of the adult nervous system.

The Feller lab studies spontaneous activity in the immature mouse retina. Mice are born with their eyes closed. During the first few weeks of postnatal development, immature retinal circuits spontaneously generate propagating bursts of action potentials, termed retinal waves. During this same postnatal period, there is a tremendous amount of development within the visual system, including formation of retinal circuits that mediate various light responses, as well as the sculpting of retinal projections to their primary targets in the brain. Hence, the developing visual system is a premier model system for studying the role of spontaneous activity in the development of functional circuits.

The first part of Dr. Feller's presentation focused on the work her lab is doing to elucidate the cellular mechanisms underlying the generation of retinal waves. In the few days prior to eye opening, the excitatory drive underlying retinal waves switches from cholinergic to glutamatergic, at which point retinal waves coexist with light responses. Using a combination of genetics, electrophysiology, and calcium imaging, researchers in the Feller lab have been able to look at the mechanisms by which developing glutamatergic circuits spontaneously generate correlated activity. This work has shown for the first time that glutamate spillover plays a role during development at the circuit level.

The second part of Dr. Feller's presentation pertained to the role of early activity and retinal waves in the development of retinal circuits. Retinal waves are detected during an extended period perinatally—from one week before birth to two weeks after birth in mice. There is a critical period of retinal development during which retinal waves and light-evoked responses coexist. To explore the interaction between vision and retinal waves, a novel multielectrode array was employed to record both spontaneous and light-evoked responses from a number of retinal ganglion cells (RGCs) simultaneously. Dr. Feller presented data describing the maturation of several different RGC types, including direction-selective RGCs and the development of the mosaic organization of receptive fields. These data indicate that even though the light response properties of individual RGCs are not mature at eye opening, cellular interactions at this point in development have already ensured the formation of nearly mature visual receptive field organization.

Anirvan Ghosh, PhD
Professor
Neurobiology Section
Division of Biology
University of California, San Diego
October 6, 2008

The Dynamics and Regulation of Synapse Formation

Like Dr. Feller's work, Dr. Ghosh's work also attempts to answer the question of how proper synapse formation takes place during development. As can be seen in this technical summary, the Ghosh laboratory employs a broad spectrum of techniques in the hunt for genetic, as well as electrophysiological, correlates of brain development.

The Ghosh lab is interested in the assembly of neural circuits. The establishment of functional neuronal circuits depends on the formation of appropriate connections between populations of neurons. To achieve this, neurons must extend axons toward target areas and then make stable synaptic connections with specific target neurons in the region. To investigate the mechanisms by which mammalian neurons select synaptic targets, the Ghosh lab utilizes hippocampal microcultures in which the formation and elimination of synapses by individual neurons can be assessed. They have found that, when given a choice of potential targets, individual dentate gyrus (DG) neurons preferentially innervate their correct CA3 targets rather than CA1 neurons and other DG neurons. DG neurons initially make synapses with all cell types but then eliminate the incorrect synapses. These observations indicate that selective synapse elimination underlies the emergence of synaptic specificity.

Another research area central to Dr. Ghosh's talk was the regulation of individual synapse stability. The establishment of neuronal circuits relies on the stabilization of functionally appropriate connections and the elimination of inappropriate ones. This process has been shown to be dependent on two types of glutamate receptors, known as AMPA and NMDA receptors. The Ghosh lab has found that the stability of presynaptic inputs is strongly correlated with the presence of postsynaptic AMPA, but not NMDA, receptors. Removal of postsynaptic AMPA receptors leads to a decrease in the number and stability of excitatory presynaptic inputs. Over-expression of AMPA receptors increases excitatory presynaptic input number and stability. In addition, over-expression of AMPA receptors along with neuroligin-1 in 293T cells is sufficient to stabilize presynaptic inputs onto heterologous cells. The ability of AMPA receptors to stabilize presynaptic inputs is not dependent on receptor-mediated current. Instead it relies on structural interactions mediated by the N-terminal domain of the AMPA receptor subunit GluR2. These observations indicate that an AMPA receptor-associated signal functions in a retrograde manner to regulate presynaptic stability.

David Anderson, PhD
Professor
Division of Biology
California Institute of Technology and
Investigator, Howard Hughes Medical Institute,
Pasadena, California
April 30, 2009

Neural Circuits for Innate Defensive Behaviors in Flies and Mice

Dr. Anderson is also interested in neural circuits, with his work incorporating the importance of neural connections in generating appropriate behavioral responses. Dr. Anderson's research and the topic of his presentation concern the question of how synaptic connections lead to proper behavior. To answer this question he uses a dual approach of studying both vertebrate and invertebrate systems. His work has contributed greatly to the field of behavioral neuroscience.

Emotions are fundamental to an animal's behavior, regardless of whether the animal in question is a simple invertebrate or a more complex mammal. Dr. Anderson's lab studies the neural circuitry and genetic interactions responsible for "emotional" behavior in both fruit flies and mice. The Anderson group has used both of these organisms to elucidate the mechanisms underlying learned or conditioned behaviors.

One such behavior, fear conditioning, has been shown to be directly attributable to a part of the brain called the amygdala in humans and other mammals. By combining genetic and electrophysiological tools with a variety of behavioral assays, Dr. Anderson and his colleagues have identified a specific population of neurons within the amygdala that is involved in gating (i.e., acting as a "brake" on) conditioned fear. Inhibiting the activity of these neurons causes an increase in fear behavior. Furthermore, these neurons are activated by drugs that attenuate fear, such as benzodiapezines (e.g., Xanax). Interestingly, these amygdala neurons receive descending connections from the prefrontal cortex, a part of the brain that has been implicated in extinguishing fear reactions in settings where they are unnecessary or counterproductive. One prevailing theory is that repeated stress can disrupt these descending connections, so that normal extinction of fear responses no longer takes place. Such disruptions may underlie affective disorders such as Post-Traumatic Stress Disorder (PTSD). Studies such as Dr. Anderson's may provide hope for PTSD patients, as manipulation of specific populations of amygdala neurons might someday be used to alleviate symptoms associated with the disorder.

Despite all that is known about learned responses such as fear conditioning, very little is known about the basis of unlearned, genetically programmed behaviors. For this reason, the Anderson lab is also trying to understand the genes and/or neural circuits that are responsible for these types of behaviors in simple model organisms. In a recent study conducted in his lab with fruit flies, researchers were able to combine genetic and functional imaging techniques with a new behavioral assay to look at the basis of a simple, innate defensive behavior. The assay has been termed the WISL assay (wind-induced suppression of locomotion), and it involves placing flies in a chamber with a light breeze. When the breeze begins, the flies immediately stop moving. As soon as the wind is stopped, the flies begin moving about again. This behavior may be a simple reflex that prevents flies from being blown away in a strong wind, or may be a primitive precursor to "fear" responses in higher organisms. The sensory basis of WISL behavior was mapped to a subset of wind-detecting neurons within the Johnston's organ, which is part of a fly's antennae. This is an important first step toward mapping the neural circuitry that underlies this innate defensive response.

Robert H. Brown Jr., MD, PhD
Professor
Harvard Medical School
Director, Day Laboratory for Neuromuscular Research
Massachusetts General Hospital
Boston, Massachusetts
September 15, 2008

Amyotrophic Lateral Sclerosis: Lessons from Genetics

The final speaker in our Colloquium Series was Dr. Robert H. Brown, who is widely known for his accomplishments in the field of neurodegenerative disease. Just as the formation of connections is crucial to proper brain development and behavior, so too is maintenance of these connections imperative for proper brain function later in life.

Dr. Brown and his lab members are renowned for their work on the inherited basis of neurodegenerative and neuromuscular diseases. Specifically, the lab has contributed to a significant number of discoveries in neuromuscular disorders, such as amyotrophic lateral sclerosis (ALS, also known as Lou Gehrig's disease) and muscular dystrophy. In 1993, Dr. Brown and his associates were the first to identify a genetic mutation that causes familial ALS cases, which has laid the groundwork for the development of the most widely studied animal model of ALS. Dr. Brown and his team have subsequently investigated other genetic variants that cause ALS and strategies for ALS therapy.

One of the hardest challenges of studying ALS is that although there are many genetic correlates, in most cases the disease is not obviously familial in any way. For this reason, in 2007 Dr. Brown became part of an initiative funded by the National Institute of Neurological Disorders and Stroke to use new and advanced genetic techniques towards furthering ALS research. The goal of the initiative was to employ genome-wide single-nucleotide polymorphism analysis in a large sample of ALS patients across the country to try to identify new gene correlates for the disease. The results of these studies have led to many new discoveries outlining the underpinnings of ALS, and may provide the basis for therapeutics and treatments in the future.

The M. R. Bauer Distinguished Lecturer Series Summaries 2008–2009

Introduction

Each year the M. R. Bauer Distinguished Lecturer Series brings to campus two eminent investigators in neuroscience. These distinguished scientists spend a full week at the Volen Center, during which time they give a public lecture and more technical presentations about their work. Of special value is the ability of our invitees to visit the laboratories of the Volen Center, with a special focus on interactions with graduate students and postdoctoral fellows. During their visits to the various labs they are able to share their knowledge and wisdom with these younger scientists.

Lorna W. Role, PhD

Professor and Chair
Department of Neurobiology and Behavior
and Center for Nervous System Disorders,
State University of New York, Stony Brook
Stony Brook, New York

Dr. Role uses molecular and biochemical approaches to understand modulatory control of synapse excitability in the mammalian brain. Her work offers important insights into synaptic function and dysfunction that may underlie neuropsychiatric disorders such as schizophrenia. Due to a scheduling difficulty, Dr. Role's visit has been postponed until September. We will describe her visit in next year's report.

Carol A. Barnes, PhD
Regents' Professor
Psychology and Neurology
Director, Evelyn F. McKnight Brain Institute
University of Arizona
Tucson, Arizona
May 18, 2009

Brain and Behavioral Aging: Molecules, Maps, and Memory

The work in the Barnes laboratory epitomizes the theme of this year's Bauer Series: connections. Although adult aging can be accompanied by some degree of loss in neuronal mass, we now know that a significant contributor to age-related cognitive change lies not in the loss of cells but in changes in synaptic strength and thus neural connectivity. Dr. Barnes has been at the forefront of research in understanding the physiological processes that underlie the cognitive changes that occur in normal aging. We were honored to have her as one of our two M. R. Bauer Distinguished Lecturers.

Aging is associated with specific impairments of learning and memory, some of which are similar to those caused by damage to the area of the brain known as the hippocampus. For example, healthy older humans, monkeys, and rats all show poorer hippocampal-dependent spatial memory than do their younger counterparts.

The search for the underlying neurobiological changes responsible for these cognitive deficits have revealed that, in fact, many biological properties of old rat hippocampal cells are quite intact, and that there is stability in hippocampal principal cell number across aging in old humans and monkeys, as well as rodents. While widespread deterioration does not occur, selective anatomical and electrophysiological changes have been found. Smaller subregions of the hippocampal cells such as the dentate gyrus and CA1 sustain either a loss in the number or a loss of the function of synapses in aged, memory-impaired rats.

The changes in connectivity of the hippocampal region during aging have been thought to contribute to observed age-related impairments of synaptic plasticity, which include the observations that long-term potentiation (LTP) is more difficult to induce in older rats, and the synaptic weights decay about twice as fast in older as in younger animals. Moreover, long-term depression and the LTP reversal are both easier to induce in aged animals. Thus, a reasonable summary in terms of the effect of normative aging processes on hippocampal plasticity mechanisms is that the balance of increasing and decreasing synaptic weights through artificial stimulation is altered during aging, possibly contributing to the observed memory impairments in older animals. Consistent with this, Dr. Barnes discussed data that indicate that the transcription of immediate early gene markers of activity and plasticity (e.g., Arc) are reduced in old hippocampal cells following behavior.

The dynamic interactions among cells in hippocampal networks are also disrupted in aged rats, as measured during ensemble recordings in freely behaving animals. These studies have demonstrated that old rats have difficulty retrieving previous representations of well-learned environments, show defective behaviorally induced place field expansion plasticity, and deficits in reactivation of experiences during sleep with preserved temporal order. Taken together, the data suggest age-related impairments in storage, retrieval, and consolidation of information. Dr. Barnes concluded her presentation by describing experiments that highlighted the specificity of changes in the aged hippocampus, pointing to the dentate gyrus in rats and monkeys as being particularly vulnerable in normal aging, a pattern that is quite distinct from that observed in Alzheimer's disease.

Volen National Center for Complex Systems Scientific Retreat 2009

On April 15–16, 2009, the Volen National Center for Complex Systems Annual Retreat was held at the Marine Biological Laboratory (MBL) in Woods Hole, Massachusetts. The MBL facilities for our retreat were excellent, with lecture halls, function rooms, cafeteria-style dining, and overnight dorm room accommodations for over one hundred Volen Center faculty members, graduate students and postdocs in attendance. The MBL also provided a perfect context for stimulating scientific discussion in a relaxing ocean-side atmosphere away from our laboratories and offices for just a little while.

As will be seen in the following summaries, a selection of Volen Center scientists (professors Piali Sengupta, Paul Miller, Robert Sekuler, and postdoctoral fellow Aki Ejima) spoke about their research and the connections that ran from the nervous systems of small insects to human learning. Our keynote speaker for this year's retreat was Professor Leslie Kay from the University of Chicago, who spoke about her work on the physiology of perception and its interaction with experience. No less important to the spirit of our retreat, it was an opportunity for our graduate students to present posters highlighting their doctoral research and for us to discover new areas for potential interlab collaborations.

Wednesday, April 15, 2009

2:00 p.m.
Arrival at MBL and Check-In

4:30 p.m.
Poster Sessions

6:00 p.m.
Dinner

7:15 p.m.
Keynote Speaker:
Leslie Kay, PhD,
University of Chicago
"Oscillatory modes and the context of early olfactory processing"

8:30 p.m.
Evening Social

Thursday, April 16, 2009

7:30 a.m.
Continental Breakfast

8:30 a.m.
Aki Ejima, PhD,
Brandeis University
"Courtship decision making is regulated by signal comparison between two olfactory pheromone pathways in *Drosophila melanogaster*."

9:15 a.m.
Piali Sengupta, PhD,
Brandeis University
"Pheromone signaling in *C. elegans*"

10:00 a.m.
Break

10:30 a.m.
Paul Miller, PhD,
Brandeis University
"Say that again. How auditory recall depends on verbal stimulus quality."

11:15 a.m.
Robert Sekuler, PhD,
Brandeis University
"Human imitation learning: Mechanisms, strategies, and ERPs"

12:15 p.m.
Lunch

1:00 p.m.
Departure

Leslie Kay, PhD
Professor
University of Chicago

Oscillatory Modes and the Context of Early Olfactory Processing

The Kay laboratory is interested in understanding how an organism connects with or perceives its surrounding environment. Specifically, its research utilizes olfactory stimuli in order to better understand this question. Behavioral assays and electrophysiology experiments allow the researchers in the Kay lab to explore not only how an animal perceives external stimuli, but also how context and experience influence that perception.

One of the most basic questions in perception is how sensing of objects in the environment is transferred into organized percepts within neural systems and within minds. This begins with objective stimuli with physical and quantifiable input patterns, quickly translated into neural representations imbued with associations, memories, and context. Dr. Kay described her work measuring the dynamical processing modes of the olfactory system using the local field potential (LFP; the cortical basis of the EEG). In the olfactory system this shows several characteristic oscillations that can be linked to various behavioral and cognitive contexts. These signals show us that the olfactory system uses at least two different modes to process odor information, and these modes are strongly influenced by the cognitive structure of the odor discrimination task.

In her presentation, Dr. Kay noted that the characteristic oscillatory patterns found in the olfactory system LFP signals are primarily in three frequency bands. Theta oscillations (2-12 Hz in waking rats and mice) follow the sensory input signal or the respiratory drive. Riding on the crest of this slower oscillation is the gamma oscillation (40-100 Hz in rats and mice), associated with odor stimulation. These oscillations are initiated at the transition from inhalation to exhalation and have been shown to be associated with odor discrimination. Beta oscillations (15-30 Hz in rats and mice) are the least studied mechanistically but have been associated with odor discrimination learning by several laboratories. Dr. Kay's lab has assessed the changes in power (amplitude) of these oscillations as rats learn several odor discriminations in specific task contexts. In a go/no-go task, rats learned to press a lever in response to one odor and to refrain from pressing in response to another odor; in a two-alternative choice task they learned to press one lever in response to one odor and to press another lever in response to another odor. LFPs were recorded from the olfactory bulb and other parts of the olfactory and hippocampal systems, including the pyriform cortex (olfactory cortex) and the hippocampus.

In the two-alternative choice task, the researchers found that when rats had to discriminate very similar odors, neural synchrony within the olfactory bulb was significantly enhanced, as evidenced by a large increase in the power of gamma oscillations associated with correct performance. These oscillations were restricted to the olfactory bulb, being absent in the closely connected pyriform cortex. With dissimilar odors, gamma oscillations were irregular during odor sniffing. While there were beta oscillations in both areas underlying the signal, there was no modulation of these with discrimination performance. In the go/no-go task there was a suppression of gamma oscillations and selective enhancement of olfactory bulb beta oscillations coincident with increasing performance on each odor set, even with the same odors used in the two-alternative choice task. Beta oscillations, unlike the gamma oscillations, were present in the pyriform cortex and the hippocampus, with the signals highly coherent between structures. These data support the notion that the olfactory system can be reconfigured to process information differently depending on the cognitive context.

Aki Ejima, PhD
Postdoctoral Fellow
Brandeis University

Courtship Decision Making Is Regulated by Signal Comparison Between Two Olfactory Pheromone Pathways in *Drosophila melanogaster*

Similar to the Sengupta lab, Dr. Ejima, working in Dr. Leslie Griffith's lab, is examining how chemical cues connect organisms. Dr. Ejima is asking how an animal connects with its complex environment to generate a suitable behavioral response. Using courtship behavior of the fruit fly as a model system, her work investigates the neural and molecular mechanisms that control innate and/or adaptive behaviors.

Courtship decision making is regulated by signal comparison between two olfactory pheromone pathways in *Drosophila melanogaster*. Aphrodisiac pheromones produced by females are a strong attractive cue to stimulate male courtship. On the other hand, *cis*-vaccenyl acetate (cVA), a product of the male ejaculatory bulb, works as a courtship inhibitory pheromone. Sensing the presence of cVA on another male avoids potential male-male courtship.

In order to examine how pheromonal information is processed in odorant receptor neurons (ORNs), Dr. Ejima's work involves physiological analysis using an activity-sensitive fluorescent marker, synaptopHluorin. This work has shown that the pheromone-sensitive ORNs receive cholinergic excitatory input to their presynaptic terminals. Blocking expression of the acetylcholine receptor in either courtship stimulatory ORNs or inhibitory ORNs diminishes cVA-responsive courtship suppression, suggesting that lateral feedback modification of ORNs is critical for pheromone coding. Intriguingly, co-suppression of the excitatory feedback in both types of ORNs rescues the cVA-response defect, indicating that the behavioral output is determined by the signal equilibrium between the two olfactory pheromone pathways. There also appears to be some adjusting mechanism that maintains the basal balance at neutral level, since over-stimulation of one pathway (e.g. by prolonged exposure to purified cVA) elicits up-regulation of the counterpart pathway, causing an enhanced level of subsequent courtship activity. This lateral communication between the two groups of ORNs might contribute to the background-noise canceling mechanism that allows a male to ignore his own smell and lead him to make an appropriate courtship decision.

Piali Sengupta, PhD
Professor
Brandeis University

Pheromone Signaling in *C. Elegans*

Just as organisms must connect with their surroundings, so too must they connect with each other. The Sengupta Lab studies how the soil nematode C. elegans *uses chemical cues (pheromones) to connect to others of its species and how these signals regulate behavior and development.*

Animals communicate with each other using visual, auditory, and chemical cues. Chemical cues are particularly complex, consisting of multiple small molecules, each of which can convey specific information. Pheromones comprise a subset of these chemical cues and are used primarily for intraspecies communication. Pheromones can elicit long-term effects on development and physiology ("primer" effects), or short-term, immediate effects on behavioral responses ("releaser" effects). The Sengupta lab is working toward identifying the molecular signaling pathways by which pheromones elicit specific context-dependent responses. Their goal is to gain a better understanding of the mechanisms by which communication between and within species regulates behavior and development

The soil nematode *Caenorhabditis elegans* secretes a complex mixture of chemicals referred to as dauer pheromone. Similar to pheromones in other species, dauer pheromone regulates both development and behavior of *C. elegans*. During the first larval stage of development, high concentrations of pheromone trigger entry into the alternate stress-resistant dauer larval stage. When conditions improve, dauer larvae exit the dauer stage and resume reproductive growth. In the adult stage, dauer pheromone regulates rapid behavioral responses such as attraction and repulsion. The molecular mechanisms by which dauer pheromone mediates these distinct responses at different developmental stages are unknown.

The Sengupta lab is currently working on identifying the molecular components that mediate the dauer regulatory effects of dauer pheromone. Their findings will allow for further investigation of how complex chemical cues elicit the appropriate responses in *C. elegans*, and will provide insights into related processes in other animals.

Paul Miller, PhD
Assistant Professor
Brandeis University

Say that Again. How Auditory Recall Depends on Verbal Stimulus Quality

Another way that organisms, in this case humans, can connect to each other is through language. Although the ease with which we communicate through language is often taken for granted, the processes behind language recognition and production are complex. Dr. Miller is using computational modeling to shed light on the neuronal connections underlying these elusive processes.

When asked to recall a list of words, older adults with hearing impairment perform worse than adults of similar age with better hearing. Interestingly, this is the case even when words are presented at a level of loudness and clarity that allows the words to be recognized correctly—albeit with some effort. If speech recognition is an "all-or-none" phenomenon (we either correctly identify a word or make a mistake), then these results give rise to the following conundrum: Why is the distinct process of laying down a memory trace of an identified word affected by the difficulty of the identification? That is to say, once a word is identified, should it not be as easily remembered as any other identified word?

In his presentation, Dr. Miller described a computational model of word recognition and recall that included some of the key underlying biological processes needed for sensory processing and memory. The simulations included groups of model neurons, some of which fire spikes in response to specific word stimuli. Connections between cells are altered by the patterns of spikes, in accordance with measurements made on brain tissue in a number of previous studies. The model is based on attractor dynamics, such that stimuli of different levels of quality can provoke network activity that is identical post-stimulus. This represents our ability to recognize a word correctly across a wide range of stimulus qualities.

Dr. Miller's model reproduces the normal findings that recall of a word in a sequence is facilitated by its association with a prior word. Importantly, the ability of the model to provide such recall is strongly dependent on the strength and speed with which prior word recognition occurs. That is, even though a weak stimulus can produce sufficient network activity to produce word recognition, the slow and weak process by which such recognition is reached produces less of the strengthening of connections to other cells that are needed for later memory recall. Dr. Miller's simulation results are supported by behavioral findings that suggest that a single word in a list masked by noise can reduce an individual's ability to recall both the prior word and the following word.

Robert Sekuler, PhD
Professor
Brandeis University

Human Imitation Learning: Mechanisms, Strategies, and EEG

As important as language is for connecting people, it is a phenomenon that is fairly unique to humans. Many organisms incapable of producing speech or language learn and communicate through imitation. The final retreat speaker, Robert Sekuler, described a number of interesting discoveries regarding imitation in the context of divided attention and cognitive resources.

Imitation—learning to perform some act by seeing it performed—plays a key role in the acquisition and fine-tuning of numerous behaviors. From a neuroscience and modeling perspective, imitation is especially challenging as it recruits multiple, overlapping networks throughout the entire human brain. Dr. Sekuler's presentation described the tasks that his laboratory have developed for the systematic study of imitation and some behavioral and electrophysiological results from those studies. One of their principal test beds has been a gesture imitation task: individuals view and then try to imitate sequences of gestures performed by a computer-generated humanoid hand; with the other main test bed, individuals view a disc that moves across a computer display along quasi-random paths and then try to reproduce the path using a stylus on a graphics tablet. In each test bed, careful design of the test stimuli has made it possible to test hypotheses about the mechanisms that support imitation.

One obstacle to progress in understanding imitation has been the challenge of quantifying the fidelity of a complex imitation. The Sekuler lab has pioneered the development of algorithms that perform this task automatically and objectively. The algorithms exploit the same spatiotemporal discontinuities that human observers have been shown to use when trying to segment some complex behavior. Imitation fidelity exhibits striking serial-order dependence, with fidelity being highest for gestures or movements that appear early in a sequence. To account for this primacy gradient and other distinctive features of imitation, including near-neighbor transposition errors, the researchers in the Sekuler lab drew upon the framework of competitive queuing, a theory whose neural underpinnings have recently attracted considerable interest and study. Recordings with high-density arrays of electroencephalographic (EEG) scalp electrodes revealed the origin of the primacy gradient. They focused on oscillatory power in two EEG frequency bands that are indices of selective attention. Power in each band decreased over the course of an entire series of movements, as successive movement segments were viewed and had to be stored in memory for later, offline imitation. These results suggest that a competition for attentional resources between the demands of visual encoding and those of memory is responsible for the primacy gradient. This discovery points the way toward techniques that could facilitate imitation learning in a variety of settings, including treatment of neurological conditions that impair imitation.

Acknowledgments

We thank the speakers who came to the Brandeis campus this past year to share with us their research and to engage in many hours of stimulating discussion and exchange of data and ideas with Volen Center faculty members, graduate students, and postdoctoral fellows. We are also grateful to our visitors for forwarding us their lecture summaries, which form the basis of this report.

We wish to especially acknowledge Justin Slawson and Sara Wasserman, graduate students in the life sciences at Brandeis, for their valuable contributions and editorial assistance in the preparation of this annual report.