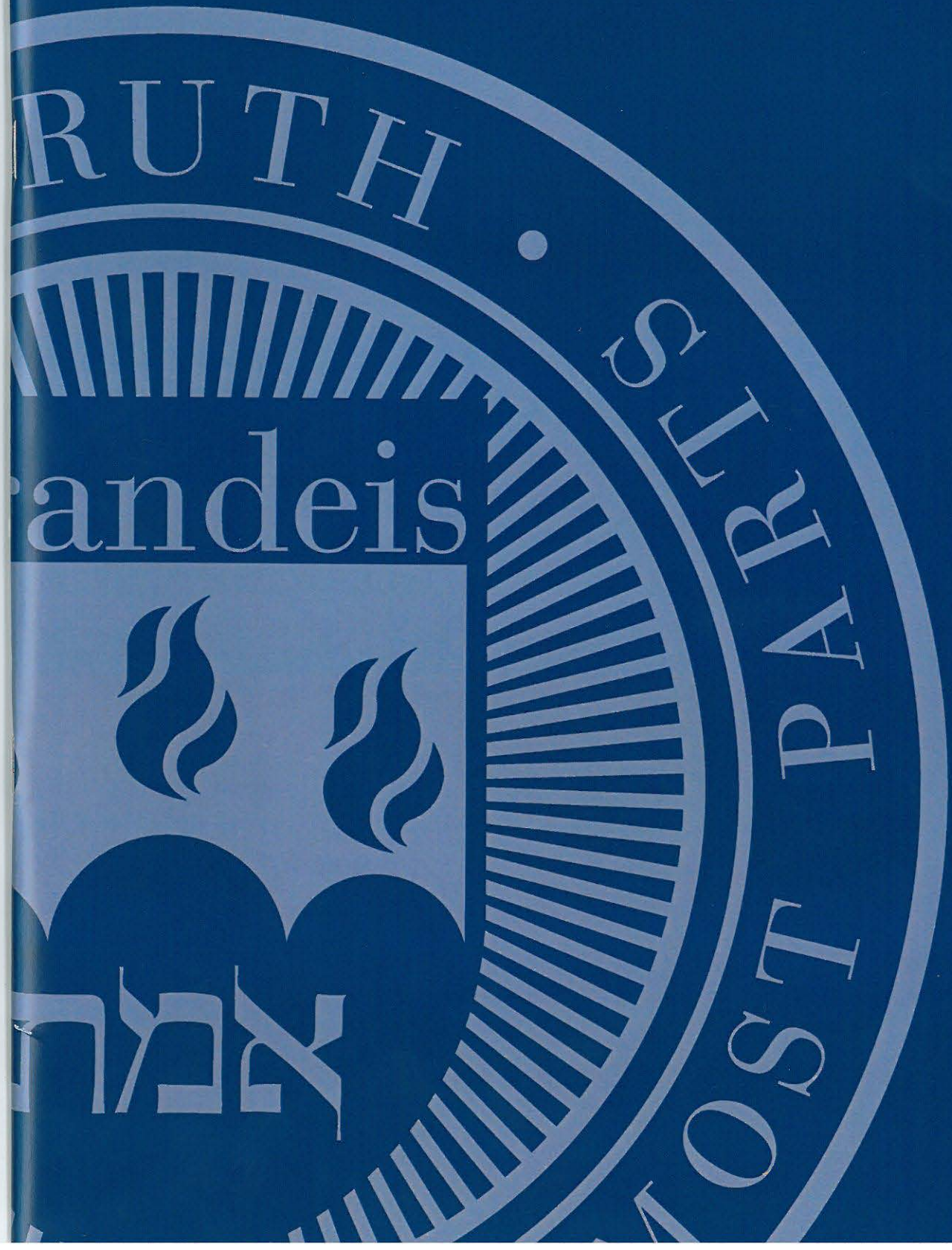
Brandeis University

Benjamin and Mae Volen National Center for Complex Systems

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

August 2012



The M.R. Bauer Foundation Colloquium Series, Annual Scientific Retreat and Distinguished Guest Lecturer Series 2011-2012 Summary

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The 2011-2012 M.R. Bauer Foundation Colloquium Series, Annual Scientific Retreat and Distinguished Guest Lecturer Series

Introduction

To paraphrase Immanuel Kant's famous saying, concepts without intuitions are empty, and intuitions without concepts are blind. Although our conceptual capacity sets human beings apart from other creatures, our sensory capacities provide the material from which concepts are made. The emergence of neuroscience in recent decades has made it possible to examine and analyze the workings of sensation in each of its modalities, and here both the similarities and the differences between humans and animals can be illuminating. The scientific study of sensation in its various forms was the overarching theme of the lectures, the colloquia and the retreat sponsored by the M.R. Bauer Foundation at the Volen National Center for Complex Systems at Brandeis University in the 2011-2012 academic year.

Traditionally, sight has been regarded as the preeminent form of sensation. But for many animals that is plainly not the case. By examining sensation in diverse species, we gain a richer, more rounded grasp of how the various modes of sensation enable living beings to make their way in the world. We gain, too, a better understanding of the mutual dependence between sensation and behavior. Not only is all this intrinsically interesting, it also enriches and deepens our understanding of the human.

What follows are summaries of twelve talks on different aspects of sensation. The topics range from the olfactory system in silkmoths to the auditory system in field crickets, from the neural mapping of space to the neural computations underlying sensorimotor control, from the organization of the visual cortex to the workings of somatosensation. Each paper as reflected in these summaries helps to advance our knowledge of the detailed workings of sensation, and each raises important questions for further research.

These talks were made possible by the generous support of the M.R. Bauer Foundation. Over the past two decades, the foundation has become a vital partner to the Volen National Center for Complex Systems. The foundation recognizes that the advancement of science takes place not only in the laboratory, but also in the seminar room and lecture hall, and in the countless conversations that help to spread ideas and spark new research. We are both pleased and fortunate to have the M.R. Bauer Foundation as such a generous and steadfast friend of the Volen Center.

Leslie Griffith, M.D., Ph.D.
Nancy Lurie Marks Professor of Neuroscience
Director, Volen National Center for Complex Systems

The M.R. Bauer Colloquium Series Summaries

Introduction

Astronomer Edwin Hubble (1889-1953) once noted that "equipped with his five senses, man explores the universe around him and calls the adventure Science." This ability to learn about, interact with and respond to the surrounding environment is an integral part of the human experience. But, in many ways, we take for granted our ability to see the sun shine, to listen to a conversation or to recognize the scent of a particular flower. Sometimes, however, these systems go wrong or, in some cases, fail to develop in their natural course. As we have learned more and more about human and animal sensory systems, we have been continually intrigued by their staggering complexity, which is nevertheless driven by elegantly simple underlying principles.

For example, in the human ear there are 12,000-15,000 hair cells, the receptors necessary for proper hearing. However, a variety of other organisms are able to accomplish equally impressive sensory feats with much simpler nervous systems. For example, the lowly fruit fly can localize sound and respond to specific courtship calls using an auditory system that is similar in structure to that of humans yet contains fewer than 500 neurons (brain cells). Drawing on such simple systems, the work of one of the speakers detailed in the following pages describes how a better understanding of audition in flies is contributing to the development of improved hearing aids for humans. This is just one example, albeit a striking one, of how the study of "model" organisms can aid in our understanding of human sensation.

The 2011-2012 M.R. Bauer Colloquium series offered insights from five distinguished scientists on how the sensory systems of several model organisms function, culminating in a better understanding of how these senses shape the "higher-order" processes of learning, memory and movement. We have arranged the order of the colloquia in accordance with the sensory modality the investigations explore — including sight, smell, hearing and touch. A theme emerges: The study of an organism even as small as the fly can provide us with valuable insight into the sensory experience of humans. As in previous years, each of the more technical summaries is preceded by a brief introduction, in italics, which places the presentation within the broad context of this year's M.R. Bauer Colloquium Series theme — the role of sensation in how humans and animals interact with the world around them.

Massimo Scanziani, Ph.D.
Center for Neural Circuits and Behavior
University of California, San Diego
(February 12, 2012)

Addressing Cortical Processing by Perturbing the Activity of Individual Layers

While many animals rely on olfaction or audition as their dominant sense, with vision occupying a subservient role, in humans and many mammals this hierarchy is reversed. At first glance, the organization of the mammalian visual system may seem difficult to understand. It turns out, however, that the primary brain region responsible for our sense of sight, the visual cortex in the posterior portion of the brain, is arranged in interconnected layers, with each layer providing a unique contribution to the visual process. In his presentation, Dr. Scanziani described the role of layer 6 in the mouse visual cortex, which modulates the intensity of the visual response. In tying together information from a variety of brain regions, layer 6 is responsible for bringing the initial steps of visual processing into focus.

Primary sensory areas in the cerebral cortex, which make up a large part of the brain in many mammals, are composed of a stack of six neuronal layers. Anatomical and physiological data indicate that these layers are interconnected via vertical excitatory axons, which send information from one neuron to another. This structure suggests that sensory processing in any given layer may be modulated by several other layers. To date, however, the exact contribution of each layer to cortical processing is poorly understood. Work in the Scanziani lab has addressed the role of layer 6 (L6) in the mouse visual cortex, whose excitatory neurons not only send axons to more superficial layers but also project to the primary sensory nuclei of the thalamus, the main source of sensory input to the cortex. L6 is thus positioned to influence cortical sensory responses through two pathways, directly via intra-cortical projections and indirectly via cortico-thalamic projections.

Using *NTSR1* Cre mice, a genetic line that selectively expresses Cre recombinase in L6 pyramidal cells, in combination with *in vivo* and *in vitro* electrophysiological approaches, the Scanziani lab has discovered that L6 controls the gain, or intensity, of visually evoked activity in neurons of the upper layers. Importantly, this gain modulation does not affect the tuning of cortical neurons to the orientation of the stimulus. This gain modulation results from the coordinated action of L6 projections to superficial layers and deep projections to the thalamus, with a substantial role of the former circuit. These observations thus establish L6 as a major mediator of cortical gain modulation and suggest it could be a node through which convergent inputs from several brain areas can regulate the earliest steps of cortical visual processing.

Kazushige Touhara, Ph.D.
Department of Integrated Biosciences
University of Tokyo
(February 27, 2012)

Narrowly-Tuned Chemoreception for Odorants and Pheromones

Scent is a powerful sensation, causing salivation in anticipation of one's favorite meal, or helping one identify a significant other by a distinct cologne or perfume. Dr. Touhara's work describes how silkmoths use odors to find food or a potential mate. Strikingly, each odor is specifically recognized by a single receptor in the olfactory ("smell") system in these insects. This ability to activate different receptors causes specific neural circuits to be mobilized, allowing the silkmoths to respond with an appropriate behavior.

Animals are attracted by general odorants derived from food or by pheromones released from the opposite sex. This chemical information is detected by chemosensory receptors expressed by peripheral olfactory sensory neurons. In his colloquium, Dr. Touhara described some examples of narrowly-tuned chemosensory receptors.

Bombykol, the first sex-pheromone to be discovered (in 1959), is released by female silkmoths and attracts males. The Touhara lab has identified the male-specific olfactory receptor in the antenna that recognizes *bombykol* with high sensitivity and selectivity. This was the first insect pheromone receptor to be identified. In the silkworm, the Touhara lab found that *cis-jasmone* emitted by their food, mulberry leaves, was a potent chemoattractant for silkworms and detected by one specific olfactory receptor in the antenna. These receptors are narrowly-tuned to *bombykol* or *cis-jasmone,* and, thus, the neural circuitry is designed to send the specific information that leads to the attractive behavior. Unlike vertebrate olfactory receptors that couple with G proteins, insect olfactory receptors consist of a heteromeric complex and comprise a novel class of ligand-activated nonselective cation channels.

The Touhara lab has also identified a gustatory receptor that specifically recognizes *D-fructose* in silkworms, and found that it was a sugar-regulated cation channel. In mice, a male-specific peptide pheromone *ESP1*, which enhances female sexual behavior, is recognized by one specific vomeronasal receptor. This receptor is expressed in the vomeronasal organ, an auxiliary olfactory organ many animals have that is used for sensitive chemical detection. The neural circuitry activated by these "specialist" narrowly-tuned chemosensory receptors appears to govern a distinct behavioral output of a pheromone or a biologically important chemosignal that is crucial for survival or mating in various animal species.

Ron Davis, Ph.D.
Department of Neuroscience
Scripps Research Institute, Florida
(March 19, 2012)

The Brain's Logic for Memory Formation and Forgetting

Many of us have had the experience of smelling a familiar scent and have been immediately transported to our memory of the place or the time we first smelled it. This powerful association between smell and memory was the topic of Dr. Davis' talk. It turns out that fruit flies have the same skill. However, it appears that scents linked to positive memories are remembered differently than scents linked to negative ones. These different mechanisms seem to encourage the brain to "forget" the negative associations while preserving the positive.

The molecular and cellular mechanisms underlying the formation and retention of memories remain largely unknown. These issues remain a difficult challenge to resolve but are of unparalleled importance since the vast majority of neuropsychiatric disorders impair memory. The Davis lab has approached these general issues by addressing two important questions: What is the logic by which the brain stores memories associated with pleasing or positive cues versus negative or aversive cues? And is there an active biological process for removing or erasing memories after they form?

The Davis lab has been able to peer into the brain of the living fruit fly, *Drosophila melanogaster,* using sophisticated imaging equipment before and after the fly learns about odor cues, and visualize the changes that occur in the brain due to learning. These changes, or memory traces, often present themselves as increases in calcium influx into specific populations of neurons in response to the learned odor. These studies, using a negative cue associated with an odor, reveal that the brain represents the odor coupled with the negative cue as multiple memory traces that form in areas of the central nervous system that process odors. The different memory traces exist for different periods of time after learning, with several traces apparently representing short-term memory, one representing intermediate-term memory, and two representing long-term memory. More recent studies have focused on odor learning coupled with a positive cue, with the underlying question of how the brain represents aversive versus positive events. The Davis lab has found that the memory traces for positive events are longer-lasting than aversive memory traces and that they exhibit broader expression in the neurons in which they form.

Memories can become stabilized after learning, or they can be forgotten. The Davis lab has recently discovered that there exists an active forgetting mechanism to erase unwanted and unimportant memories. Dopamine signaling is required for learning about odors in the fly at the time that the odor is learned. Surprisingly, dopamine neurons remain active after learning and mediate the forgetting signal. Thus, the brain is designed to learn information but also to actively forget using the dopamine signal, unless what is learned is so important that it overrides the forgetting signal.

David Julius, Ph.D.
Department of Physiology
University of California, San Francisco
(December 12, 2011)

From Peppers to Pit Vipers: Molecular Mechanisms of Temperature and Pain Sensation

The ways in which we "feel" pressure, temperature, pain or even the position of our own bodies are all controlled by different sets of neurons. In his presentation, Dr. Julius described work from his lab that has shown that our sense of touch is still more finely segregated: Different receptors detect hot and cold, and these temperature extremes are "felt" by different sets of neurons, too. Moreover, animals like pit vipers can "sense" infrared, thanks to another set of receptors and neurons that humans do not have.

Our sense of touch — also known as somatosensation — encompasses a diverse repertoire of sensory modalities that includes proprioception (sense of the position of our own bodies), mechanosensation (pressure), thermosensation (temperature) and nociception (pain). As such, somatosensory neurons and their downstream central circuits are tasked with the job of detecting, transmitting and interpreting a broad collection of environmental and endogenous stimuli of both a physical and chemical nature. To accomplish this, primary afferent somatosensory neurons, which carry information to the brain, are equipped with a diverse group of cell surface receptors and ion channels that endow them with specialized receptive properties, and that ultimately define the biophysical, pharmacological and psychophysical properties of what is arguably the most complex and multifaceted of sensory systems.

In the past 15 or so years, we have seen tremendous progress in the identification of the molecules, mechanisms and neural pathways underlying somatosensation. This is especially true in regard to understanding the initial events of stimulus detection by sensory nerve fibers and their communication with neurons of the spinal cord dorsal horn. In this lecture, Dr. Julius focused primarily on mechanisms underlying thermosensation, the sensation of temperature, with an emphasis on evolutionary adaptations that have enabled diverse organisms to exploit a common molecular strategy for sensing ambient temperature.

The Julius lab has shown that members of the Transient Receptor Potential (TRP) ion channel family are chiefly responsible for detecting ambient temperature. TRPV1 (the receptor for capsaicin, a compound found in such foods as peppers) detects thermal stimuli in the noxiously hot range (>43°C), and TRPM8 (the menthol receptor) detects stimuli in the cool to cold range (<25°C). In mice, primary afferent neurons that express these channels are mostly (but not entirely) segregated into distinct subpopulations, arguing for a "labeled line" system, in which hot and cold stimuli are conveyed to the central nervous system (CNS) through distinct circuits. How these signals are sorted (or merged) at the level of the spinal cord is currently unknown.

How is temperature detected in animals that maintain distinct core body temperatures (e.g., warm-blooded homeotherms versus cold-blooded poikilotherms)? The Julius lab has shown that TRP channels in these organisms differ in their thermal activation profiles in a manner that parallels their core body temperatures, demonstrating evolutionary adaptation of thermosensory receptors. Some animals have taken thermosensation to the extreme by evolving specialized somatosensory organs capable of detecting infrared (IR) radiation. Three types of snakes (pit vipers, boas and pythons) and one mammal (vampire bats) possess heat-sensing "pit organs" that are devoted to IR sensation. The Julius lab has shown that somatosensory nerve fibers innervating these pit organs express receptors that are very similar to the TRP channels described above and/or splice variants having exceptionally low activation thresholds (<30°C), making them well suited to the task of detecting infrared heat from predators or prey. These studies have provided interesting new insights into the genetic mechanisms underlying sensory adaptation and the molecular tuning of thermosensory receptors.

Philip N. Sabes, Ph.D.
Department of Physiology
University of California, San Francisco
(December 5, 2011)

Sensorimotor Integration and Learning: Linking Neural Circuits and Behavior

How our sense of touch and our motor systems work together to shape our perception of the world is represented in this final colloquium series summary. The questions asked are basic to many of our everyday motor activities but no less intriguing. For example, as one reaches for the coffee mug on one's desk, the brain learns its location, and subsequent reaching for the mug becomes more efficient. The same thing happens with Major League Baseball pitchers, whose fastball release points have a standard deviation of about 1 inch. Yet how does this seemingly automatic learning occur? In his presentation to the Volen Center community, Dr. Sabes described his work measuring and modeling how the brain flexibly and adaptively integrates information for movement control.

Once fully developed, humans interact flexibly and effortlessly with the world around them. For example, the combination of perception and action needed to reach for objects in the local environment seems entirely rote. But this ease belies the complex and sophisticated nature of the computations required for even such simple acts. In their laboratory, the Sabes group has been studying these computations from a combined behavioral, physiological and theoretical perspective. In this colloquium, Dr. Sabes focused on his work describing the remarkably plastic nature of human sensorimotor control, with the goal of linking his theoretical explanations of why people behave the way they do to physiological descriptions of the underlying neural circuits.

Most voluntary actions rely on neural circuits that map sensory cues onto appropriate motor responses. One might expect that for everyday movements, like reaching, this mapping would remain stable over time, at least in the absence of error feedback. However, this is not the case. In the first part of his colloquium, Dr. Sabes described a simple and novel psychophysical phenomenon in which recent experience shapes the statistical properties of reaching. Specifically, when recent movements are made to targets near a particular location, subsequent movements to that location become less variable but at the cost of increased bias for reaches to other targets. This process exhibits the variance-bias tradeoff that is a hallmark of Bayesian estimation. The Sabes lab provides evidence that this process reflects a fast trial-by-trial learning of the prior distribution of targets. They have also shown that these results may reflect an emergent property of associative learning in neural circuits. Finally, they demonstrate that adding Hebbian learning to a model network for reach planning leads to a continuous modification of network connections that biases network dynamics toward activity patterns associated with recent inputs. This learning process quantitatively captures the effect that recent experience has on the variance-bias tradeoff in their psychophysical data. This network also provides a good approximation to a Bayesian estimator. These observations illustrate how associative learning can incorporate recent experience into ongoing computations in a statistically principled way.

In the second part of this colloquium, Dr. Sabes focused on the relationship between neural activity in the cerebral cortex, movement variability and learning. It is currently understood that neural variability gives rise to behavioral variability. However, the Sabes lab has shown that neural variability in cortical motor planning areas only weakly predicts trial-by-trial fluctuations in reaching movements. Instead, these areas contribute to movement variability through a slow, random drift in neural activity patterns (across hundreds of movements) that is linked to a parallel drift in movement metrics. Both the behavioral and neural drifts are strikingly captured by a simple model in which noise continually accumulates in a (non-optimal) online learning process. The Sabes lab has also shown that the behavioral drifts they see in macaque monkeys are present on the same timescales in highly skilled athletes performing well-trained movements. In particular, Major League Baseball pitchers show a very similar random drift in their pitching performance across a baseball game. This shows (perhaps paradoxically) that an error corrective learning process may drive this performance drift and may represent the fundamental limit on how precisely the brain can control movements, even for elite athletes. The hope is to better understand ways in which consistent and coordinated movements are produced in the face of environmental variability and changes in one's internal state.

The M.R. Bauer Distinguished Lecturer Series Summaries 2011-2012

Introduction

Every year, the M.R. Bauer Distinguished Lecturer program brings to campus two distinguished visitors who spend a full week at Brandeis. These visitors present talks to small and large groups, visit center laboratories, and engage students, postdoctoral fellows and faculty in informational and highly interactive conversations about shared areas of research interests. This year, our distinguished lecturers were Ron Hoy from Cornell University and Carla Shatz from Stanford University.

Ron Hoy, Ph.D.
Department of Neurobiology and Behavior
Cornell University
(Week of October 31, 2011)

Another Fly Story: (Ir-/Ear) Relevance in the Age of Translational Research

Our first weeklong visitor, Ron Hoy, has provided new insight into understanding our sense of hearing. Speaking, singing and laughing are forms of auditory communication that we use to express ourselves to others. Vocalizations are important to many other animals, too, such as the male field cricket that performs mating calls to attract females. However, these calls are also sensed by the parasitic fly, Ormia ochracea, whose auditory organ allows it to sense and locate its host over a vast area. Dr. Hoy's research in understanding the biophysics of how the Ormia auditory organ functions has led to new advances in the production of microphones for hearing aids, increasing their sensitivity and directional acuity. This research demonstrates once again how very basic questions can lead to advancements in medical technology on a human scale.

We vocalize whenever we speak or sing. Vocalization is language made audible, and the goal is to make ourselves understood to (an)other human being(s) — in essence, to communicate. Many animals also communicate through the use of audible signals, as we know from the beautiful songs of birds and the croaking of frogs and toads, as well as the howling of dogs and monkeys. These are all true vocalizations produced in social contexts. Many insects also produce audible signals, such as the chirps and trills of crickets, katydids and cicadas; like the calls of birds and frogs, they serve similar social behavioral functions such as to facilitate mating and to ward off competitors for territory. Such diverse and unrelated animals have all converged on sonic signals for communication.

Communication in biological systems is much like communication in any medium or context. Signals are transmitted between senders and receivers that pass through a medium of exchange; there are "rules" of syntax and semantics that are either built into the nervous system (through genetics and development) or are learned in an adaptive way, usually through a critical period. It is not completely understood how human speech and comprehension is processed in the human brain, so some bioacousticians have turned to animals that have simpler nervous systems. One such model system is biocommunication in crickets, in which males call to attract females that hear, and hone in on, the singing male; females are mute. Crickets, like many animals, including other insects, frogs and some birds, communicate via innate and stereotypical acoustic signals that are pulsatile and species-specific. Behavioral experiments in nature or in the laboratory reveal that both sender and receiver are "tuned" to these call rhythms, and in the case of crickets this tuning is genetically encoded. It comes about through adaptations in the biomechanics of signal production and auditory sensitivity and acuity. The stereotyped species-specificity comes about through tuning of the neuroacoustic systems that underlie both call production in the sender and its perception/recognition in the receiver. Thus, the "syntax" and "semantics" of mating calls is under genetic control. The nature of the coupling is still controversial but is thought to be related to the central pattern generator (CPG) that sets the properties of the sender's motoric act of call production. It is thought that the conspecific female also possesses the CPG that functions as a reference "template" that she uses to compare songs and that underlies the "recognition" of her own species song.

It is conceivable that something along these lines explains the coevolution between conspecific senders and receivers of adaptive signals such as species-specific mating calls.

A more unusual situation occurs when one species "breaks the code," so to speak, of the mating signal of another species. Such an occurrence seems to have happened between the tachinid fly, *Ormia ochracea,* and field crickets of various species. The biological context for this "code-breaking" is very familiar: that which exists between a parasite and its host, which also has a high degree of biological specificity. A case in point is the way in which the parasitic fly senses and finds its host, a calling male cricket — a case of acoustic parasitism, an extreme rarity in the animal kingdom.

Given that many species of flies — most famously, *Drosophila melanogaster* — display acoustic signals as part of their mating rituals, what is so special about another species of fly, albeit a parasitic one, using the hearing of acoustic signals to detect and locate a host? It's all about the ears. *Drosophila* and all other known fly species have "ears" that operate at close distances, within a few body lengths, millimeters to centimeters. But for *Ormia* to hear crickets, its ears must be able to detect cricket songs at great distances — tens of meters or more, on the wing and high in the air — far away from a chirping cricket, singing from his burrow in fields and lawns. The standard-issue "fly-ear" of *Drosophila* just won't do. To hear like a cricket, this fly needs the ears of a cricket. Evolutionarily speaking, this is a tall order. In this colloquium, Dr. Hoy focused on just how the *Ormia* fly has managed to do this — to reinvent a cricket's ear. In so doing, the fly has evolved an even better auditory organ — more sensitive and more directionally acute than a cricket's. It turns out that an *Ormia* fly had to surmount some very unfavorable physics owing to its small size. It is, after all, much smaller than a cricket. Physicists tell us that, in matters of sound detection and localization, being bigger in size means being better able to process sound cues for directional sound localization. The Hoy lab discovered how *Ormia* solved the size issue through evolutionary innovation: Its ear is unlike the ears of other insects or other animals. *Ormia*'s ears reveal some "neat" biomechanical innovations and behavioral ones as well. The auditory organ of this fly is a bioacoustical marvel with some unexpected practical implications. The "design features" of *Ormia*'s ear have drawn the attention of acoustical engineers who saw an opportunity to "copy" *Ormia*'s eardrums using nanotechnology to produce silicon analogs of the ears to produce nanoscale directional microphones for hearing aids. These *Ormia*-inspired microphones offer breakthroughs in sensitivity and directional acuity, in addition to being robust and inexpensive to produce.

Ormia's story is another instance of what can happen when investigators follow their "nose" to solve a basic biological mystery involving animals and behaviors that seem to have nothing to do with the "real" world. However, in pursuing these questions the investigators are led to a completely unexpected payoff that may lead to a technological breakthrough in the domain of medical prosthesis — in this case, improved hearing aid microphones for the hearing impaired. The experience of the Hoy lab is an old story in science but one worth repeating in an age where basic research questions are placed on a scale tilted toward direct applications and short-term benefits.

Carla Shatz, Ph.D.
Department of Biology and Neurobiology
Director, Bio-X
Stanford University
(Week of April 23, 2012)

Dynamic Interplay Between Nature and Nurture in Brain Wiring

Our second distinguished lecturer, Carla Shatz, returned to the topic of vision, giving two lectures on visual system development at the cellular level and neural plasticity. She showed how insights gained from this work can go beyond vision, per se, to have potential implications for human disease, such as recovery from stroke and neurodevelopmental disorders such as autism.

Over the course of two lectures, Dr. Shatz discussed examples of how neural activity — initially spontaneously generated, and at later ages driven by sensory experience — contributes to the shaping and tuning of neural circuits during critical periods of brain development. Her lectures focused on the development of the mammalian visual system and specifically considered the connections from the retina, which first detects visual information in the eye; to lateral geniculate nucleus (LGN), the first point of visual processing in the brain; to primary visual cortex, where "higher-order" visual processing occurs in the brain. These connections begin to form early in life — in utero in many species — and well before the onset of vision. Initially, a basic wiring plan from eye to brain is established using strictly determined axon guidance cues that direct neurons to synapse on, or form connections with, the appropriate targets. This period is followed by a prolonged phase of activity-dependent development in which initially diffuse synaptic connections are fine-tuned to yield the final highly precise circuits present in the adult brain. This tuning process is thought to occur throughout the brain during development, endowing it with a vast capacity to adapt to the environment and also underlying the brain's ability to learn throughout life.

In the visual system, neurons called retinal ganglion cells from each eye connect to LGN neurons in adjacent eye-specific layers. LGN neurons representing each eye, in turn, connect to neurons in layer 4 of primary visual cortex to form the alternating system of ocular dominance (OD) columns, regions of the cortex that respond preferentially to one eye or the other. But during development, eye inputs are intermixed; the adult LGN layering or cortical OD columns then form as connections remodel. Remodeling requires ganglion cell signaling. Blocking action potentials, the electrical signals that allow neurons to communicate with one another, prevents eye-specific layering and also alters the patterning of OD columns. Dr. Shatz's first lecture presented the discovery that the retina generates its own spontaneous activity long before vision starts. Ganglion cells in the eye fire synchronously in "waves" that sweep across retinal domains. Moreover, these retinal waves are needed for ganglion cell axons to segregate into eye-specific layers in the LGN: Blocking them prevents segregation, while altering the spatiotemporal pattern of waves perturbs segregation. It is as if the eye is running "test patterns" on the brain to check for correct connections weeks before the onset of vision. Thus, the brain internally generates highly coordinated patterns of neural activity early in development, even before sensory input.

In her second lecture, Dr. Shatz presented the idea that there are signaling pathways that oppose or "brake" synaptic plasticity, in addition to molecular pathways such as MAP kinase signaling and CREB-mediated transcription that enable activity-dependent plasticity. One such "brake" was uncovered in an unbiased screen searching for genes in the LGN regulated by the endogenous activity driven by retinal waves. Unexpectedly, members of the MHC Class I gene family (the HLA genes in humans) were found to be expressed in neurons and regulated by neural activity and visual experience. The discovery was especially surprising because it was thought previously that neurons do not express MHC Class I genes under normal conditions due to the brain's "immune privilege," which isolates the brain from the immune system utilized by the rest of the body. To assess requirements for MHCI in the CNS, the LGN was examined in knockout mice in which the MHCI gene is not expressed: Eye-specific layers do not form, and synapse regression fails to occur. What's more — contrary to the usual situation following gene knockout, in which synaptic plasticity is abolished — in the MHCI mutant mice there is greater synaptic strengthening than normal. In particular, OD plasticity is enhanced in visual cortex, a form of synaptic strengthening known as long-term potentiation (LTP) is 150 percent larger than in mice that have MHCI, and a form of synaptic weakening known as long-term depression (LTD) is absent. These observations suggest that MHCI molecules might act as *negative* regulators of synaptic plasticity — rather like a "molecular brake."

In the immune system, certain MHCI family members function in cell-mediated immunity by interacting with a variety of receptors on immune cells, the most famous of which is T-cell receptor (TCR). Similar receptors on neurons could interact with neuronal MHCI and carry out activity-dependent synaptic processes. In a systematic search for receptors known to bind MHC Class I (MHCI) proteins in the innate immune system, the Shatz lab found that mRNA for PirB, an Ig-like transmembrane receptor, is highly expressed in neurons in many regions of the mouse brain, particularly in cerebral cortex, olfactory bulb and cerebellum. The Shatz lab generated mutant mice lacking PirB function and discovered that the extent of OD plasticity in visual cortex is *increased*. Thus, PirB, like its MHCI ligands, appears to function to limit the extent of synaptic plasticity in the CNS. Together, these experiments imply that this family of immune molecules, thought previously to function only in the immune system, may also work at neuronal synapses to limit how much — or perhaps how quickly — synapse strength changes in response to new experience. These molecules may be crucial for controlling circuit excitability and stability in the developing as well as the adult brain. Removing them in mice not only generates enhanced cortical plasticity but also permits more rapid recovery from stroke, and changes in their function may even contribute to developmental disorders such as autism and schizophrenia.

Volen National Center for Complex Systems Scientific Retreat, 2012

On April 2, 2012, the Volen National Center for Complex Systems held its annual scientific retreat. The theme, "Spatial Knowledge and Movement," centered on the work of this year's keynote speakers: Edvard and May-Britt Moser, of the Kavli Institute for Systems Neuroscience, Norway. In a departure from our usual practice of off-campus retreats, the retreat this year took place on campus, with talks held in the Shapiro Campus Center and the poster session and end-of-the-day social hour held in the atrium of the new Shapiro Science Center. As always, these scientific retreats allow our students and faculty to take a break from their daily activities, broaden their perspectives and enjoy the company of their colleagues. Through these retreats, new collaborations among Volen Center faculty often arise.

In addition to our two keynote speakers, we heard from three of our Brandeis researchers: Paul DiZio, Jeff Gelles and Zvonimir Dogic, from the departments of psychology, biochemistry and physics, respectively. As is apparent in the summaries that follow, the 2012 scientific retreat represented a stimulating cross-section of the work being conducted on sensation and movement from several levels of analysis — from human motor control to macromolecular motion.

Monday, April 2, 2012

9:00-10:00 a.m.
Arrival and breakfast

10:05-10:15 a.m.
Arthur Wingfield, D.Phil.
Nancy Lurie Marks Professor of Neuroscience
Director, Volen National Center for Complex Systems

10:15-11:15 a.m.
Edvard Moser, Ph.D.
Director, Kavli Institute for Systems Neuroscience
Norwegian University of Science and Technology
Trondheim, Norway
"Grid Cells and the Entorhinal Map of Space"

11:15 a.m.-Noon
Paul DiZio, Ph.D.
Associate Professor of Psychology and Volen National Center for Complex Systems
Brandeis University
"Reaching in Space"

Noon-1:30 p.m.
Lunch
Hassenfeld Conference Center

1:30-2:30 p.m.
May-Britt Moser, Ph.D.
Co-Director, Kavli Institute for Systems Neuroscience
Norwegian University of Science and Technology
Trondheim, Norway
"Entorhinal-Hippocampal Interactions and the Neural Basis of Memory"

2:30-3:15 p.m.
Jeff Gelles, Ph.D.
Aron and Imre Tauber Professor of Biochemistry and Molecular Pharmacology
Brandeis University
"Mechanism(s) of a Molecular Motor"

3:15-4:00 p.m.
Zvonimir Dogic, Ph.D.
Associate Professor of Physics
Brandeis University
"From Isolated Molecular Motors to Synthetic Cilia and Beyond"

4:00-5:00 p.m.
Poster session, mingling and drinks
Shapiro Science Center
Brandeis University

Edvard Moser, Ph.D.
Director, Kavli Institute for Systems Neuroscience
Norwegian University of Science and Technology

Grid Cells and the Entorhinal Map of Space

The focus of Dr. Moser's talk was an exploration of the neural substrate of our "sense" of space. Spatial behavior has been investigated experimentally for more than 100 years. Edward Tolman was the first to suggest that animals and humans form maps of the external environment and use these both to navigate from one location to another and to create a scaffold for the representation of an experience. Evidence for Tolman's ideas came with the discovery of place cells, neurons that fire only when an animal is in a particular place, in the 1970s, and more recently with the discovery of a universal metric component for the spatial map in the 2000s.

Work from Dr. Moser's lab has shown how the entorhinal cortex and hippocampus of the mammalian brain form a continuously updated map of external space that includes both present and past information. The work suggests that cells in the entorhinal cortex are part of a universally applicable map for space, consisting of multiple functionally specialized cell types entangled in a complex neural network. A key cell type in this network is the grid cell — a cell type that the Moser lab discovered in the entorhinal cortex in 2005. Grid cells fire selectively at regularly spaced positions in the environment such that, for each cell, activity is observed only when the animal is at places that together define a repeating triangular pattern tiling the entire environment covered by the animal, much like the holes of a Chinese checkerboard. The spatially periodic activity pattern of grid cells defines distances as well as directions, suggesting that grid cells are part of the brain's metric for space.

A key objective of Dr. Moser's lecture was to discuss the structural and functional organization of the entorhinal grid map. It is known that the scale of the grid map is topographical in that the spacing of the grid increases from the dorsal to the ventral end of medial entorhinal cortex. Dr. Moser presented new data suggesting that the organization of the grid map is modular, consisting of noncontinuous clusters of cells that differ in grid spacing and grid orientation. Multisite recordings covering more than 50 percent of medial entorhinal cortex show that there are at least four discrete modules, beginning with grid cells with small grid spacings most dorsally and ending with modules with large spacing values most ventrally. There is considerable anatomical overlap between the modules. The actual values for grid spacing differ between animals, which explains why grid spacing appears to increase gradually in group-averaged data. Boundaries between grid spacing modules correspond to boundaries between orientation modules. Changes in the environment, such as the displacement of a wall, may affect one grid module but not another, suggesting that the modules are functionally independent. The organization of grid cells into modules that respond differentially to external input is a potential source for the orthogonalization of place maps — with each map coming to consist of an entirely distinct group of cells — in the hippocampus.

Paul DiZio, Ph.D.
Associate Professor of Psychology and
Volen National Center for Complex Systems
Brandeis University

Reaching in Space

Knowledge of one's position in space — realizing where your arm is pointing when your eyes are closed, or reaching for an object without over- or undershooting — are among those functions we usually take for granted. That is, of course, unless these automatic-seeming functions fail, such as in the case of loss of vestibular function, neurological disease or stroke. Dr. DiZio's presentation of his research on control of reaching movements illustrated these themes.

Dr. DiZio spoke about the work he and his colleagues are conducting that examines effects on perception and motor control under centrifugal forces generated by placing a person in a rotating room. Reaching movements made in a rotating room are affected by Coriolis forces that are directly proportional to the cross product of the room's angular velocity and the arm's linear velocity within the room. Coriolis force perturbations in the rotating room are transient (only present when the arm is moving), unexpected and unique because they act without local contact. They have found that reaching movements deviate in the direction of Coriolis forces in the rotating room but that adaptation occurs within 10-20 movements such that straight, accurate reaches are again possible and mirror-image aftereffects occur when rotation stops. This work has shown that the nervous system represents and utilizes detailed "expectations" about the forces that will be encountered during a reaching movement, and the movement plan is more dynamic than many had originally assumed.

May-Britt Moser, Ph.D.
Co-Director, Kavli Institute for Systems Neuroscience
Norwegian University of Science and Technology

Entorhinal-Hippocampal Interactions and the Neural Basis of Memory

Building on the talk presented by Dr. Edvard Moser in the morning, Dr. May-Britt Moser, our afternoon keynote speaker, continued the discussion of the brain's memory of external space. Each point in the external environment corresponds to its own set of place cells, but how is that system established? Dr. Moser described the converging signals that come together to tell a place cell when — or, rather, where — to fire. In addition, Dr. Moser discussed recent findings that help to explain how these cells map new environments. In other words, we have a better understanding of how an unfamiliar location can become familiar as we spend time there.

The entorhinal cortex, together with the hippocampus, is a key component of the mammalian brain's system for mapping of external space. Neuronal recordings from the hippocampus showed in the 1970s that the majority of principal cells in this region have distinct spatial firing correlates. These so-called "place cells" were shown to fire only when the rat visited certain locations. The origin of the place cell signal remained elusive for more than 30 years, but the Mosers' discovery of grid cells in 2005 provided some clues.

In her talk, Dr. Moser suggested that while grid cells are likely the predominant source of place signals, they may not be the only ones. She first showed that grid cells co-localize with other functional cell types such as head-direction cells and border cells, which each contribute to a dynamically updated metric representation of current location in the medial entorhinal cortex. She then presented data from a study using a combined optogenetic-electrophysiological strategy to determine the functional identity of entorhinal cells with monosynaptic projections to the place-cell population in the hippocampus — that is, a single entorhinal cell signals to a signal place cell. Microbial opsins were expressed selectively in the hippocampus, targeting a subset of entorhinal projection neurons. Virally transduced cells were identified in medial entorhinal cortex as cells that fired in response to local flashes of light. The most responsive cells were grid cells, but short-latency firing was also induced in border cells and a small fraction of head-direction cells, suggesting that place cells are generated by convergence of signals from multiple entorhinal cell types.

The final part of Dr. Moser's talk dealt with the representation of space in memory. An important difference between grid cells and place cells is the tendency for place cells to form orthogonal representations in different environments — that is, the group of cells that fires in one environment is entirely distinct from the group that fires in another environment. This orthogonalization process is thought to depend on the formation of attractor states in recurrent neuronal networks — the firing of one neuron recruits the firing of other neurons to contribute to the total representation of a given place. While several experimental observations are consistent with the presence of attractors in the entorhinal cortex and hippocampus, the dynamic processes supporting attractor dynamics, at the time scale of behavior, are not well understood. Dr. Moser showed that, in response to an instantaneous transition between two familiar and similar spatial contexts, hippocampal CA3 networks undergo short periods of competitive flickering between preformed representations before settling in on the representation most consistent with the new cue configuration, several seconds after the cue change. The data suggest that, in CA3, pattern completion dynamics take place within an individual theta cycle. The repetition across cycles may facilitate error correction, thus enhancing the discriminative power of the system in the presence of conflicting input cues from spatial representations in entorhinal cortex and stored representations within the hippocampus.

Jeff Gelles, Ph.D.
Aron and Imre Tauber Professor
of Biochemistry and Molecular
Pharmacology
Brandeis University

Mechanism(s) of a Molecular Motor

The first three speakers addressed motor movement in observable human and animal behavior. Dr. Gelles described his research on a different kind of movement, one that is equally essential to proper biological function. This is referred to as macromolecular motion, which is critical for the proper biological functions of enzymes and nucleic acids.

A major focus of the Gelles lab is the study of motor enzymes: molecular "machines" that catalyze a chemical reaction, capture the free energy released by the reaction and use this energy to perform biologically useful mechanical work. Motor enzymes play essential roles in diverse biological processes ranging from muscle contraction, to neuronal development, to mitosis, to gene transcription. To learn how the enzymes work, the Gelles lab studies them *in vitro* using molecular cloning, enzymology, protein chemistry and biophysical chemistry techniques. The laboratory has also pioneered methods for visualizing nanometer-scale movements and individual chemical reaction events in single enzyme molecules. Such methods reveal the crucial dynamic features of enzyme mechanisms that are missing from the information produced by static techniques like X-ray crystallography.

Zvonimir Dogic, Ph.D.
Associate Professor of Physics
Brandeis University

From Isolated Molecular Motors to Synthetic Cilia and Beyond

Our final retreat speaker prior to the poster session was Dr. Zvonimir Dogic of the physics department. He discussed the source of the movement patterns of cilia and flagella that, as he describes it, "propel entire cells or move fluids across the surface of various tissues." The work of the Dogic lab reflects a cutting-edge synthesis of statistical mechanics, computer simulations, biochemistry, protein purification techniques and molecular cloning.

From enabling the motility of simple organisms called protists to determining the left- or right-handedness of more complex organisms, structures called cilia and flagella are present and essential for the reproduction and survival of many biological organisms. Each cilium is a remarkably complex filamentous structure assembled from about 600 different proteins with exquisite precision and reproducibility. When supplied with ATP, a sort of molecular "energy," cilia and flagella exhibit spontaneous beating patterns that either propel entire cells or move fluids across the surface of various tissues. It is a formidable and challenging task to experimentally determine the exact role of all the constituent proteins within one cilium or flagellum. Due to their intricate structure, most studies, spanning dozens of laboratories and many decades of work, approached this task by removing specific proteins from the intact organelle, in order to identify structural components that are essential for the generation of beating patterns. Despite these extensive studies, the exact mechanism by which individual components conspire together to control ciliary beating patterns remains unknown.

Dr. Dogic described a diametrically opposite approach to studying the dynamic behavior of cilia. Instead of deconstructing a fully functional organelle from the top down, his lab systematically engineers synthetic cilia-like structures from the bottom up. Specifically, they assemble microtubule filaments, molecular motors, interfilament crosslinkers and other components into synthetic structures that have reproducible, controllable and periodic beating patterns. The feasibility of this novel approach is demonstrated by preliminary results, in which synthetic bundles exhibit cilia-like beating patterns. In parallel with experimental efforts, the Dogic lab also studies the same phenomena using computer simulations. Because of the large parameter space, the simulations are an essential guide for the experiments, and, in turn, the experimental results will validate and further refine the simulation efforts. Taken together, these synergistic studies hold promise to reveal general design principles required for engineering synthetic cilia as well as understanding the biological ones.

2012 Poster Session: Presenters and Titles

The poster sessions are often the liveliest of retreat activities because, centered on ongoing research in the various laboratories represented, they allow for active interactions among faculty, students and postdoctoral fellows. This year, 13 poster presentations spanned the full range of neuroscience in the Volen Center, from systems and cellular physiology through computational and cognitive neuroscience. The titles, which we list below, give a flavor of the range of research currently ongoing in Volen Center laboratories.

Jonathan Caplan and Tilman Kispersky, "Increase in sodium conductance decreases firing rate and gain in model neurons."

Bethany Christmann, "Investigating the functional connections of the *Drosophila* memory system."

Hayim Dar, "Reconsidering recall: Inter-subject differences and the meaning of conditional response probabilities."

Alexander Flyax, "The role of DNA methyltransferases in the late development of cortical fast-spiking interneurons."

Kyle Harrington, "The effects of finite population and selection on the emergence of signaling."

Anna Moore, "Sema4D drives the rapid assembly of GABAergic synapses."

Aram Raissi, "The role of class 4 semaphorins in synapse formation."

Anatoly Rinberg, "Probing neural network robustness through temperature perturbations."

Chad Rogers, "Dramatic false perception in older adults: Metacognitive evidence from vision and audition."

Honi Sanders, "NMDA and GABA-B: The perfect couple."

Pavel Sountsov, "Probabilistic inference and learning in a spiking neural network."

Stephen Van Hooser, "Development of direction selectivity across the layers of primary visual cortex."

Christopher Vecsey, "Electrophysiological effects of the *Drosophila* neuropeptides PDF and sNPF."

Acknowledgments

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

We especially acknowledge two of our graduate students in neuroscience, Amy E. Ghiretti and Maria Genco, for their valuable contributions and editorial assistance in the preparation of this report.

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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