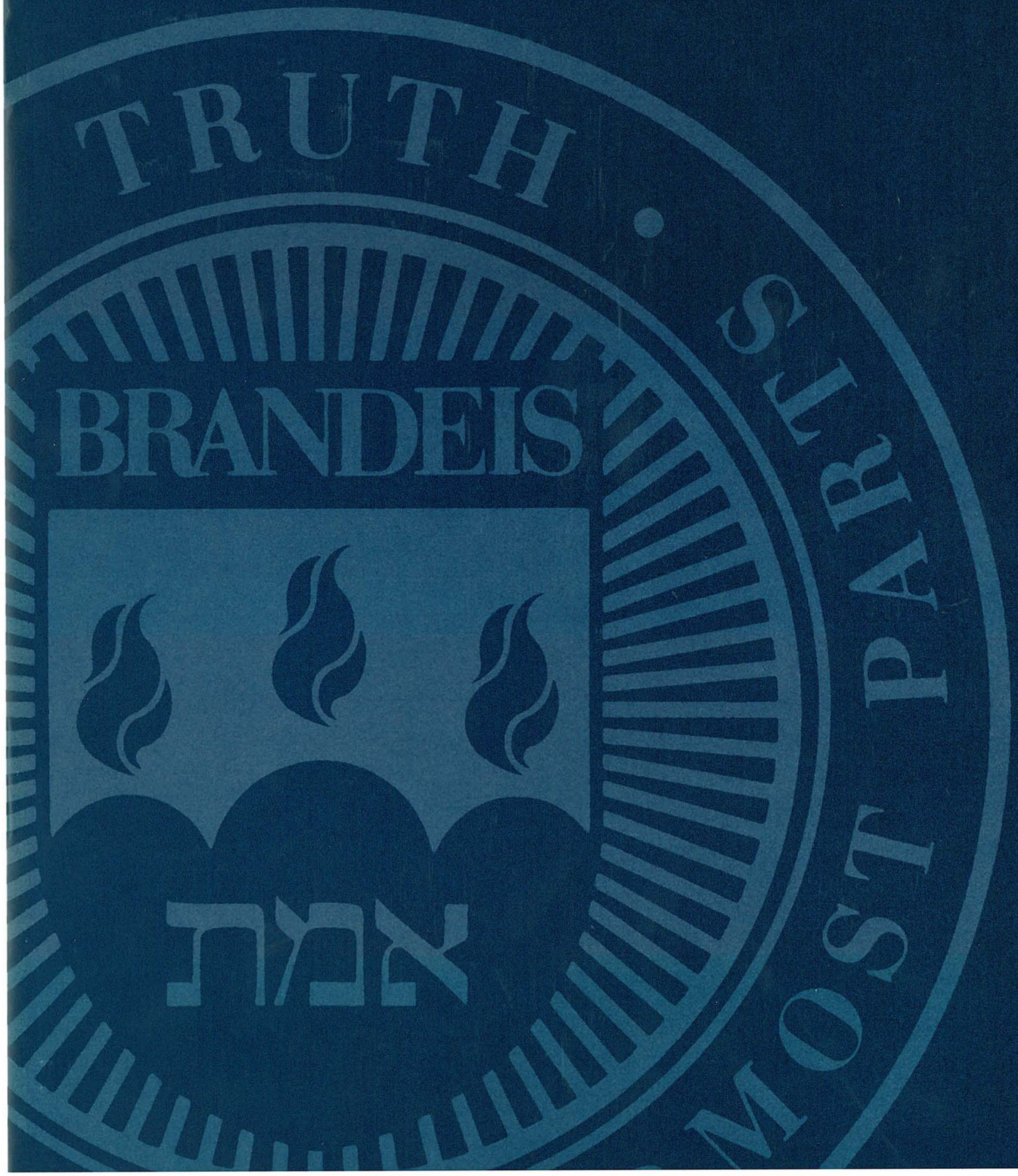
Brandeis University

Benjamin and Mae Volen National
Center for Complex Systems

# The M.R. Bauer Foundation Colloquium Series and Scientific Retreat

August 1996



# Introduction

## The 1996 M.R. Bauer Foundation Colloquium Series and Scientific Retreat

**Brandeis University**

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

The boundaries where scientific disciplines meet continue to be the most exciting areas of discovery, collaboration, and innovation. With this in mind, Brandeis University created the Benjamin and Mae Volen National Center for Complex Systems to bring together scientists from several disciplines for a shared purpose—to gain a better understanding of the brain, intelligence, and advanced computation. Not only a basic research facility, the Volen Center serves an educational role. Undergraduate and graduate students work in laboratories alongside faculty members and attend classes in the Center's lecture facilities. Another important component of the Center's educational function is the M.R. Bauer Colloquium Series.

For the second consecutive year, the M.R. Bauer Foundation has provided generous support to underwrite a series of on-campus colloquia, as well as an annual retreat, in conjunction with scientific activities at the Volen Center. These colloquia bring prominent researchers from the biological and computer sciences to campus to discuss their work, to meet with faculty members and students, and to share emerging ideas and methodologies. The retreat provides Brandeis scientists and students, as well as invited guests, with an opportunity to gather for a day or two of lively discussions, research presentations, and professional camaraderie.

During 1994-95, the inaugural year of Bauer support, five guest lecturers were invited to speak on campus as part of the colloquium series. In 1995-96, the Bauer Series welcomed seven lecturers who spoke on topics such as the impact of molecular genetics on the field of psychiatry, the areas of the brain associated with memory, and the influence of genetic variation on the sense of taste. In April 1996, the Volen Center held its annual retreat at Woods Hole, Massachusetts. As in 1995, several presentations were made focusing on work being done by some of the Volen Center's newest faculty members. All those in attendance—faculty, graduate students, and postdoctoral researchers—enjoyed discussing their research and learning more about current trends in other disciplines.

The M.R. Bauer Colloquium Series and the Volen Center retreat are important conduits for the exchange of scientific information across traditional academic boundaries. These events bring members of the Brandeis community into contact with members of the broader scientific community to share ideas and to gain new and different perspectives on their own research. These proceedings have been published to further that effort.

Irwin B. Levitan
Nancy Lurie Marks Professor of Developmental Neuroscience
Director, Volen National Center for Complex Systems

**Table of Contents**

**Samuel H. Barondes, M.D.**
Professor
Department of Psychiatry
University of California,
San Francisco
San Francisco, California
October 12, 1995

# Will Molecular Genetics Really Change Psychiatry?

**Biographical Information**
Samuel H. Barondes, M.D., received his medical degree from Columbia University College of Physicians and Surgeons in 1958, and was then an intern at the Peter Bent Brigham Hospital in Boston from 1958 to 1960. From 1960 to 1963, he was a research fellow at the National Institutes of Health in Bethesda, Maryland, where he learned biochemistry and molecular biology in the laboratory of Nobel Laureate Marshall Nirenberg. He then returned to the Boston area as a resident in psychiatry at McLean Hospital and Massachusetts General Hospital from 1963 to 1966, and has spent the remainder of his career in psychiatry departments. He was at the Albert Einstein College of Medicine in New York from 1966 to 1969, at the University of California at San Diego School of Medicine from 1969 to 1986, and since 1986 he has been at the University of California at San Francisco School of Medicine (UCSF). He was chair of the Department of Psychiatry at UCSF and director of the Langley Porter Psychiatric Institute from 1986 to 1994. Since 1994, he has been director of the Center for Neurobiology and Psychiatry at UCSF. In 1966 Barondes was the first to introduce biochemistry and molecular biology to psychiatry departments. Today it is still rare to find faculty members in psychiatry departments who do this kind of basic research. He has worked on organisms ranging from slime molds through mollusks and rodents to humans, and has made substantial contributions in every area in which he has worked. During the last five years he has turned his attention to the molecular genetics of mental illness, with particular focus on the genetics of manic-depressive disorder. He has written widely on the evolution of biological psychiatry, and on the impact that modern molecular genetics can have on psychiatry.

**Biological Psychiatry**
Barondes began by reminding the audience that the best known of all psychiatrists, Sigmund Freud, was at heart a biologist (in fact he referred to himself repeatedly in his writings as a neuropathologist). However, Freud's efforts to explain mental processes in biological terms were never successful, and he turned to analysis when he despaired of ever having enough biological information about the brain to understand mentation. Under Freud's leadership, psychoanalysis flourished, and was the main therapeutic tool of psychiatrists through much of the 20th century.

After the overview and perspective on the conflict between psychoanalysis and biological psychiatry, Barondes turned to an examination of manic-depressive illness, which together with its more common cousin, severe depression, affects a very large percentage of our population. He provided several fascinating case histories of manic depressive illness to illustrate its course, and then launched into a discussion of drugs that have proven to be very effective in its treatment.

First, he described the discovery that lithium could be an effective treatment for manic-depressive illness. This discovery, like so many important discoveries in the biological sciences, was serendipitous. Pharmacologist John Cade noted that lithium injections made guinea pigs lethargic, and concluded that lithium might be an effective treatment for the manic phase of manic-depressive disorder. This description of the first test of lithium in therapeutic doses in a manic-depressive patient was a compelling part of Barondes's lecture. It is now known that lithium blocks an inositol trisphosphate phosphatase, thus preventing the regeneration of phosphatidylinositol-bis-phosphate, an essential second messenger molecule in the nervous system. Although it is not known with certainty that this effect of lithium is responsible for its therapeutic actions, it seems likely that it does play a role. However, an important finding that remains unexplained is that lithium blocks this phosphatase immediately upon administration, whereas the therapeutic effect of lithium in manic-depressive illness takes several weeks to become apparent.

Barondes also discussed the antidepressants, which are blockers of the re-uptake of the neurotransmitters norepinephrine and serotonin. Imipramine was the first of these re-uptake blocker antidepressants,

introduced for therapeutic purposes in 1957. The most effective antidepressants today are blockers of serotonin uptake, including Prozac, which was introduced in 1987. Prozac works as well as Imipramine, and has more limited side effects. In addition, Prozac and its relatives have the completely unexpected benefit of alleviating the symptoms of a variety of neuroses. During the last five years, Prozac has, to a large extent, displaced analysis as a treatment for neurosis, even among those psychiatrists who were previously committed psychoanalysts.

Finally, Barondes discussed the next potentially great biological trend in psychiatry, molecular genetics. He emphasized that the use of molecular genetics in the diagnosis and treatment of psychiatric disorders is only in its infancy, but he has every expectation that it will have enormous impact. One problem is that the genetics of many human diseases, including psychiatric disorders, may be very complex, making them exceptionally difficult to study. However, Barondes is convinced that the influence of genetics on the way we think about psychiatric disorders cannot be overemphasized. He and his colleagues have been studying several family pedigrees in which manic-depressive illness occurs with astonishingly high frequency. They have localized a gene contributing to this trait to a relatively small region of the human genome, and are engaged in a concerted effort to clone and characterize this gene. Success in this effort will open a new chapter in biological psychiatry.

**Markus Meister, Ph.D.**
Associate Professor
Department of Cellular and Developmental Biology
Harvard University
Cambridge, Massachusetts
November 2, 1995

## The Neural Code of the Retina

The overall goal of our research is to understand how the eye conveys visual information to the brain via the electrical signals of the optic nerve fibers. Our research proposal set two specific goals: to identify the key features of this electrical activity, and what messages they carry about the visual scene: this amounts to "breaking the code" used by the retina; and to understand how this code is generated by the neural circuits of the retina.

**Concerted Signaling by the Retina**
We are continuing our investigations of concerted firing among optic nerve fibers. As reported previously, nearby retinal ganglion cells of the salamander tend to fire synchronously (within ca 10 ms of each other) much more frequently than expected by chance. Such strong correlations are mostly found between cells of the same functional type. The effect decreases exponentially with distance between the two cells, with a length constant of about 200 mm. A more detailed analysis showed that ganglion cells are coupled not only in a pairwise fashion; rather, the phenomenon involves larger groups of cells firing in synchrony, up to seven neurons at a time in our recordings. It also became apparent that the concerted firing patterns persisted under a broad range of visual stimuli, accounting for about 50 percent of all action potentials recorded from the ganglion cells. This suggested that they play an important role in visual signaling, and two extreme hypotheses could be formulated: (a) If two ganglion cells carry the same spike trains most of the time, then their signals are obviously redundant;

thus the population of ganglion cells would collectively convey much less information than one might estimate on the basis of the classical single-cell recordings from these neurons; (b) alternatively, each cell might participate in several different firing patterns, and each such pattern of synchronous spikes might carry a very specific visual message; in this case, the range of messages that the retina conveys to the brain might in fact be much richer than expected from the single-cell studies.

Recently, we have obtained evidence for the latter view. Statistical analysis showed that an individual ganglion cell does, in fact, contribute to several different firing patterns, each of which typically accounts for only a small fraction of its activity. Thus one finds many more multi-neuron firing patterns than ganglion cells. We then measured the visual receptive field of each firing pattern by reverse correlation to a random flicker stimulus (Meister, et al. *Journal of Neuroscience Methods 51*, 95-106, 1994). As a rule, the receptive field of a synchronous pair of spikes from two cells was distinct from and smaller than the receptive fields of each cell firing alone; it generally fell into the overlap region between the two individual receptive fields. The receptive fields of firing patterns involving more than two neurons were often even more sharply defined in space. We suggest that the synchronous firing patterns are caused by shared excitatory input from a presynaptic neuron, such as an amacrine cell; spikes in this amacrine cell lead to synchronous firing among all the ganglion cells it feeds. In this view, each distinct firing pattern identifies the activity of a distinct amacrine cell, and its receptive field is simply the receptive field of that amacrine cell.

Although these neurons do not project fibers through the optic nerve, the neural circuits receiving the optic nerve signals could identify an amacrine cell's activity by detecting its characteristic pattern of synchronous firing among ganglion cells. In a sense, the signals of amacrine cells might be "multiplexed" on top of the ganglion cell signals. In this way, the brain could obtain a representation of the visual scene of greater spatial resolution than expected from the classical single-neuron analysis of visual signaling. To test this idea quantitatively, we measured the information conveyed by a small group of ganglion cells about a randomly modulated visual stimulus (Warland and Meister, 1995). For this purpose we used a simple decoding algorithm, based on linear filtering of the spike trains, to reconstruct the visual scene from the ganglion cell responses. Pairs of cells that engaged in coincident firing often conveyed independent information about the visual stimulus, even though their receptive fields overlapped to a great extent. It was found that the optimal decoder of these spike trains assigned a different visual message to coincident spikes over single spikes, thus improving the reconstruction significantly. We conclude that the full meaning of the message the retina sends to the brain can only be recovered by considering the concerted firing patterns among ganglion cells. In particular, multi-neuronal firing patterns can encode spatial information distinct from that conveyed by individual neurons.

**Adaptation of the Retinal Code**

Our work over the coming year will focus on the dynamic alterations in retinal function in response to the visual environment. For example, it is well known that the retina adapts to changes in the mean intensity of the visual scene. Clearly this is advantageous because of the large daily changes in overall illumination. On the other hand, we also encounter visual environments that differ strongly in other image statistics, such as the mean contrast (difference between dark and bright regions), or the spatial correlation (the size of a typical blob of uniform intensity). Does the retina adapt its function dynamically to these image statistics? These questions are being pursued vigorously by Stelios Smirnakis and Michael Berry, a post-doc who recently joined the lab. They have already yielded intriguing results (Smirnakis et al., 1995a, 1995b), and will further our understanding of plasticity in neural circuits.

**Linda M. Bartoshuk, Ph.D.**
Professor
Department of Surgery
Yale University School of Medicine
New Haven, Connecticut
February 29, 1996

# The Sweet Tooth and Hot Peppers: Genetic Variation in the Sense of Taste

## Introduction

In the last decade, studies using approaches from molecular biology have substantially advanced our understanding of the early events in olfaction and taste. Of the four taste qualities that humans recognize, salty and sour tastes involve ion channels in the membrane of receptor cells while sweet and bitter tastes result from binding to receptor proteins. The roles that taste and smell play in the world of the newborn are very different from those of adults. Acceptance of sweet and rejection of bitter appear to be hard-wired while the affect associated with odors depends much more on experience. Genetic variation may produce total losses or losses specific to certain stimuli. Clinical studies, some of which Bartoshuk described, reveal pathologies responsible for these total or partial losses. Three cranial nerves carry taste and two of those nerves inhibit one another such that damage to one disinhibits the other and preserves overall taste function.

## Genetics of Taste

Taste worlds of humans vary because of taste blindness to phenylthiocarbamide (PTC) and its chemical relative, 6-n-propylthiouracil (PROP). Bartoshuk reviewed early PTC studies and applied modern statistical analyses, showing that a higher frequency of women tasted PTC crystals, and were tasters (threshold classification).

In Bartoshuk's laboratory, sensory scaling of PROP bitterness identified a subset of tasters ("supertasters") who rate PROP as intensely bitter. Supertasters also perceive stronger tastes from a variety of bitter and sweet substances, and perceive more burn from oral irritants (alcohol and capsaicin). The density of taste receptors on the anterior tongue (fungiform papillae, taste buds) correlate significantly with perceived bitterness of PROP and support the supertaster concept. Psychophysical data from Bartoshuk's lab also show a sex effect: women are supertasters more frequently than men. The anatomical data also support the sex difference: women have more fungiform papillae and more taste buds.

It is well known that the ability to taste low concentrations of PROP and related bitter compounds such as PTC and caffeine is heritable. Bartoshuk and her colleagues set out to determine whether the distribution of PROP taste thresholds is consistent with an additive or a dominant mode of Mendelian transmission. To that end, they determined the lowest concentration of PROP detectable by 1015 subjects and tested models of bi- or tri-modal distributions of PROP taste thresholds. The model with the greatest likelihood had three distributions and followed an additive model of PROP taste sensitivity.

## Studies of Taste after Nerve Damage

Patients with localized damage to the taste system often experience no subjective change in real-world taste experience. In an effort to understand this, eight patients who recently underwent acoustic neuroma removal were evaluated for taste loss. Localized taste testing showed that taste intensities decreased in the distribution of cranial nerve VII ipsilateral to tumor removal as expected, but asymmetries occurred for IX. Intensities were greater on the side contralateral to the tumor removal. In addition, palatal taste, also thought to be mediated by VII, was not totally abolished. It is concluded that cranial nerve IX is normally inhibited by cranial nerve VII in the taste network. When VII is damaged, this inhibition is abolished. This release of inhibition, Bartoshuk suggested, serves as a compensation mechanism that preserves normal taste experience.

## Studies of Taste Interactions (capsaicin adaptation)

The desensitization effects on taste resulting from application of 100 or 10 ppm capsaicin, accompanied by daily testing of a capsaicin series (1-1000 ppm, in log steps), or the desensitization resulting from application of 100 ppm capsaicin without the daily capsaicin testing, were investigated. The taste stimuli were three concentrations each of NaCl, sucrose, citric acid, quinine and 6-n- propylthiouracil. Following either type of 100 ppm desensitization, the magnitude estimates of the two bitter tastes, in particular, and citric acid showed significant decrements.

Following 10 ppm capsaicin or an ethanol control procedure, there were no such effects. Recovery was complete in one to three days. Bartoshuk suggested that the taste decrements are due to effects on both the taste and tactile components of taste, though there is a stronger case for effects on the tactile component.

**Studies of Pain Management**

Pain from oral mucositis afflicts 40 to 70 percent of patients receiving chemotherapy or radiation therapy. Current methods of clinical pain management (for example, topical anesthetics, systemic analgesics) have limited success. In a pilot study, Bartoshuk and her colleagues showed that oral capsaicin provided temporary relief of oral mucositis pain, which is a common side-effect of radiation therapy. Capsaicin, the active ingredient in chili peppers, is known to desensitize some neurons and has been shown to offer moderate pain relief when applied to the skin surface. Bartoshuk and colleagues found that oral capsaicin in a candy vehicle (taffy) produced substantial pain reduction in 11 patients with oral mucositis pain from cancer therapy. Although this pain relief was not complete for most patients and was only temporary, Bartoshuk believes it may be potentially quite useful as a therapeutic tool.

**Dan Margoliash, Ph.D.**
Professor
Department of Organismal Biology and Anatomy
University of Chicago
Chicago, Illinois
March 21, 1996

## Functional Organization of the Bird Song System: Implications for How, What's Learned Where

Bird song and its neurobiological substrates are central topics in ethology and neuroethology. Birds learn their songs from external tutors, and have an elaborate system of forebrain, mid-brain, and brainstem nuclei involved in aspects of song memorization, learning, perception, and production. Behavioral studies have identified critical elements of the theory of song learning, but the neural implementation of this theory has yet to be described. A connectionist modeling study has demonstrated that neurons in the nucleus ovoidalis, part of the ascending auditory system, exhibit responses to complex stimuli, such as song, that can be predicted from the neurons' responses to simple stimuli, such as tone and noise bursts. Thus, there is no evidence that the auditory response properties of these neurons are modified by the song learning process.

Indeed, to date the modification of neural sensory structures that must accompany song memorization early in life has yet to be described. A recent 2DG study suggests field L (which receives from ovoidalis and projects to HVc) may be an attractive candidate structure. In contrast, there is strong evidence that the forebrain nucleus HVc is a site of sensorimotor integration in the birdsong system. Auditory neurons in the HVc of all species tested respond selectively to the individual bird's own (autogenous) song, including neurons that exhibit strict temporal combination sensitivity. The parameters of autogenous song are specified by environmental influences during vocal learning, hence it is hypothesized that the HVc neurons shape, and are shaped by, the sensorimotor phase of learning. The representation of autogenous song has unusual features, including a global synchrony related to syllabic features of the song. These features vary between individuals, emphasizing the idiosyncratic nature of neural representations of such forms of complex learning.

The syllabic representation at the level of HVc is also observed in single neuron activity recorded during singing in zebra finch. HVc neurons have a motor recruitment activity pattern that is specific for each syllable type, independent of syllable position, and varies from neuron to neuron. Thus, during production HVc neurons encode for syllable identity.

The syllable is a motor program, generally involving all syringeal muscles, and co-articulation with the vocal tract, respiratory, and postural systems. Hence, the code at the level of HVc is not muscle based. Elucidation of the HVc code in the adult, and its establishment during sensorimotor development, will be of major importance for determining the neural mechanisms of idiosyncratic learning. Understanding the mapping between the auditory response and motor recruitment properties of the same HVc neurons remains a major theoretical challenge—how is auditory feedback used to guide vocal learning if it has no apparent relation to the ongoing motor program at the physiological level? To date, however, these same properties have yet to be

assessed in juvenile birds. The motor recruitment properties of neurons in RA, which is the major forebrain output structure and receives from HVc, differ dramatically from those of HVc neurons. RA neurons exhibit highly synchronized bursts of activity associated with sub-syllabic acoustic features such as notes. Thus, there is a hierarchical organization of the motor system that is related to the hierarchical organization of the segmental temporal structure of the vocalizations. The analysis of the mechanisms of syringeal action will be essential for a deep understanding of coding in this system.


## Larry R. Squire, Ph.D.

Professor
Departments of Neuroscience and Psychiatry
University of California School of Medicine
San Diego, California

April 11, 1996

# Memory Systems of the Brain

**Biographical Information**

Larry Squire received his B.A. in psychology from Oberlin College in 1963 and his Ph.D. in psychology from the Massachusetts Institute of Technology in 1968. He is currently a professor of psychiatry and neurosciences at the University of California, School of Medicine, San Diego. Squire is also a research career scientist at the VA Medical Center in San Diego, and the author or coauthor of 244 publications.


**Abstract**

Squire has been a leader and pioneer in studying how memory traces are organized in the mammalian brain. In his lecture he summarized studies that point to the existence of multiple forms of memory. There is an explicit or declarative memory for facts and events, and a non-declarative or implicit memory for skills and habits. Part of the evidence that leads to this distinction is the fact that declarative memories are specifically affected in amnesia, whereas non-declarative memories are spared. Squire summarized groundbreaking work in this area, based on human patients with specific and highly localized lesions within the limbic system of the brain. These studies have pointed to the hippocampus and related structures within the limbic system as being critical for the organization of new memories. Important concepts that have arisen during the course of this work include the demonstration that declarative memory changes gradually over a very long period of time, resulting in long term consolidation and the well-established phenomenon of retrograde amnesia.

One of the great strengths of Squire's approach is the parallel use of two experimental systems. He has taken advantage of the existence of populations of human patients who exhibit amnesia as a result of trauma or other damage to specific brain regions. At the same time, he has used non-human primates, whose behavioral repertoire is substantial, which can be manipulated experimentally by directed lesions. Results from each experimental system have suggested novel experimental approaches in the parallel system, yielding a stunning series of studies that have advanced our knowledge of the organization of memory in the brain.

## Geoffrey R. Loftus, Ph.D.
Professor
Department of Psychology
University of Washington
Seattle, Washington and
Department of Brain and Cognitive Sciences
Massachusetts Institute of Technology
Cambridge, Massachusetts
April 25, 1996

# A Theory of Visual Information Acquisition and Visual Phenomenology

In his presentation, Geoffrey Loftus described a theory of visual information acquisition and visual memory. The theory has two major components. First, the visual systems initial sensory response to a short duration, low-contrast stimulus is generated by a linear, low-pass temporal filter that operates on the stimulus temporal waveform. Second, information is acquired from the stimulus through an independent sampling process, whose sampling rate at time *t* following stimulus onset is jointly proportional to (a) the magnitude by which the sensory response exceeds some threshold and (b) the proportion of still unacquired information. The theory was successfully tested in five variants of a digit recall task in which temporal waveform of the stimulus was systematically manipulated. In a final experiment, the theory simultaneously accounted for performance in detection and identification tasks. Implications for visual information processing, low-contrast detection, and binocular combination of information were discussed.

## Geoffrey Hinton, Ph.D.
Professor
Department of Computer Science
University of Toronto
Toronto, Canada
May 2, 1996

# Helmholtz Machines

**Biographical Information**
Geoffrey Hinton received his B.A. in experimental psychology from Cambridge in 1970 and his Ph.D. in artificial intelligence from Edinburgh in 1978. He is currently a fellow of the Canadian Institute for Advanced Research and professor of computer science and psychology at the University of Toronto. He conducts research on ways neural networks can be used for learning, memory, perception, and symbol processing, and has over 100 publications in these areas. He was one of the researchers who introduced the back-propagation algorithm that is used widely for practical applications. His other contributions to neural network research include Boltzmann machines, distributed representations, time-delay neural nets, mixtures of experts, and Helmholtz machines.

**Abstract**
The brain learns to convert the sensory input into internal representations of the causes of the input. It does this without having a teacher to specify what each internal neuron ought to be doing. Hinton then proceeded to describe the "wake-sleep" algorithm, which uses top-down connections to create target states for the internal neurons. These target states can be used to train the bottom-up connections. The learning rule is entirely local. The performance of the system can be improved by using adaptive lateral connections within each layer to ensure that the different parts of the representation in that layer are mutually consistent.

His talk also described joint work with Peter Dayan, Brendan Frey, Quaid Morris, and Radford Neal.

# The 1996 Volen National Center for Complex Systems Scientific Retreat

**Sponsored by the M.R. Bauer Foundation**

# The Center for Complex Systems: New Directions

**Marine Biological Laboratory**
**Woods Hole, Massachusetts**
**April 8-9, 1996**

On April 8 and 9, 1996, the Volen National Center for Complex Systems held its annual scientific retreat. This year for the first time the retreat was an overnight event held at the Marine Biological Laboratory (MBL), in Woods Hole, Massachusetts. The MBL facility includes lecture halls, function rooms, cafeteria-style dining, and overnight dorm room accommodations. Bringing the researchers together off-campus for a 24-hour retreat was tremendously successful. The MBL provided a stimulating environment for interactions between the faculty, post-docs and graduate students, as well as a scenic site for walking and relaxing. Over 100 people attended this year's retreat, which consisted of a poster session, a keynote speaker, and talks by four of the Center's new junior faculty.

**Monday, April 8, 1996**

**2:00 pm**
Arrival and check-in

**4:30 pm**
Poster session and refreshments

**7:15 pm**
"Regulation of Excitability in the Auditory System"
**Keynote Speaker**
Len Kaczmarek, Ph.D.
Yale University School of Medicine

**8:30 pm**
Music and dancing

**Tuesday, April 9, 1996**

**7:00 am**
Breakfast

**8:30 am**
"Activity-Dependent Modification of Neuronal Firing Properties"
Gina Turrigiano
Assistant Professor of Biology and Volen National Center for Complex Systems
Brandeis University

**9:15 am**
"Slowly Inactivating Potassium Currents and Cortical Dynamics"
Xiao-Jing Wang
Assistant Professor of Physics and Volen National Center for Complex Systems
Brandeis University

**10:00 am**
Break

**10:30 am**
"Development and Function of Chemosensory Neurons in *C. elegans*"
Piali Sengupta
Assistant Professor of Neurobiology and Volen National Center for Complex Systems
Brandeis University

**11:15 am**
"Issues in Human Movement Control Raised by Studies in Unusual Force Environments"
Paul DiZio
Assistant Professor of Psychology and Volen National Center for Complex Systems
Brandeis University

**12:15 pm**
Lunch

**1:00 pm**
Departure

**Len K. Kaczmarek, Ph.D.**
Professor
Department of Pharmacology
Yale University School of Medicine
New Haven, Connecticut

## Regulation of Excitability in the Auditory System

Kaczmarek's studies of ion channel properties encompass cell physiological, molecular, and computational approaches. Thus his work was deemed to be ideal for the retreat, because of the diversity of interests and approaches of members of the Volen National Center for Complex Systems.

Kaczmarek began his lecture by summarizing studies on the cloning and characterization of a variety of neuronal potassium channels. These include channels with very different kinetic properties that can influence in diverse ways the activity of the cells in which they are found. Kaczmarek has also produced computational models of ion channel activity that faithfully reproduce the biophysical properties of the biological channels. He then went on to describe experiments on ion channels in neurons of the mammalian auditory system. Auditory neurons must be specialized to respond to inputs of widely varying frequency, and Kaczmarek demonstrated that this can be attributed to the particular complement of voltage-dependent potassium channels present in sub-classes of auditory neurons. In particular, the inactivation kinetics of the potassium channels play a major role in the cell physiology of the neurons. Again, he brought computational approaches into play to demonstrate the role of potassium channels with particular properties in auditory neuron physiology. The use of realistic computational models, which are based at every stage on the real biology of the neurons and on the biophysical properties of the ion channels, provide new insight and understanding into the way the brain uses specific ion channel molecules to help encode auditory stimuli.

**Gina Turrigiano, Ph.D.**
Assistant Professor of Biology and
Volen National Center for Complex Systems
Brandeis University
Waltham, Massachusetts

## Activity-Dependent Modification of Neuronal Firing Properties

Maintaining the correct balance of inhibition and excitation is extremely important for normal cortical function. Too little inhibition can lead to epileptiform activity, whereas too much inhibition can severely depress cortical responsiveness. This suggests that the balance of inhibition and excitation in cortical circuits should be tightly regulated. In visual cortex, activity has been shown to affect expression of the inhibitory neurotransmitter GABA in a manner consistent with a role in balancing excitation and inhibition; blocking activity in one eye leads to a down-regulation of GABA in the corresponding ocular dominance columns. These data suggest that the level of activity is acting through some feedback signal to locally adjust the strength of cortical inhibition, although the mechanisms by which this occurs remains unclear. A culture system is used to explore the role of activity in the control of cortical inhibition. We have found that blocking activity in culture leads to a reversible decrease in the number of neurons immunopositive for GABA, and that this decrease can be prevented by the coapplication of brain-derived neurotrophic factor (BDNF). This data suggests that activity levels can continuously adjust cortical inhibition in a bi-directional manner through a BDNF-dependent mechanism.

Primary visual cortical cultures were prepared from postnatal (P4-P6) Long-Evans rat pups. Cultures begin to show signs of synaptic activity after three to four days in vitro, and over the next few days develop spontaneous firing. After seven to 13 days, in vitro cultures were fixed and processed for double-label indirect immunofluorescence against GABA and the neuronal marker. The percentage of neurons in each culture that were GABA-positive was then calculated. Blockade of neuronal activity for two days with TTX resulted in a decrease in the percentage of GABA-positive neurons in visual cortical cultures, to about 70 percent of control values. This reduction was statistically significant ($p<0.01$, student's test). The total number of neurons in these cultures was not reduced by incubation with TTX, or by the other manipulations described below.

The neurotrophins, including BDNF, are a class of factors that have been shown to affect a diverse set of neuronal properties, including survival, outgrowth, and synaptic strengths. The expression of BDNF in hippocampal and cortical cultures has been shown to be activity-dependent; high activity levels lead to increased BDNF expression in striatal neurons. These observations suggested to us that BDNF secretion might be the signal linking changing activity levels to the expression of GABA in visual cortical cultures. In support of this hypothesis, we found that BDNF prevented the TTX-induced reduction in the number of GABAergic neurons. BDNF + TTX was significantly different from TTX alone ($p<0.01$), and was not significantly different from control. BDNF alone produced no

significant increase in the percentage of GABA positive neurons, suggesting that with activity at control values endogenous BDNF levels are saturating for this effect. This effect was specific to BDNF; Nerve Growth factor failed to prevent the TTX-induced reduction in GABA. Incubation with K252a, an inhibitor of neurotrophin receptors, produced a decrease in the percentage of GABAergic neurons comparable to that produced by TTX. These data indicate that BDNF can prevent the activity-dependent decrease in GABA-positive neurons in cortical cultures, and suggests that activity-dependent BDNF secretion may be the mechanism by which activity regulates GABA levels.

The effects of activity blockade on GABA expression was reversible. When cultures were treated for two days with TTX, then washed to remove TTX, the percentage of GABA positive neurons partially reverted to about 85 percent of control values. Concurrent incubation with BDNF during the wash completely reversed the decrease. This data has two interesting implications. First, since new neurons are no longer being generated in cultures from this age, activity must be reversibly decreasing GABA expression by interneurons rather than selectively decreasing interneuron survival. Second, these data suggest that activity can continuously and bi-directionally adjust the level of GABA expression in cortical cultures, through the regulation of BDNF levels. Such a mechanism may be crucial for allowing cortical circuits to remain within the correct operating range despite developmental or learning-related changes in synaptic strengths.

Another factor that could contribute to the regulation of activity levels is the strength of inhibitory or excitatory synapses. The strength and number of synaptic inputs onto neurons can change dramatically during development or learning, thus altering the total amount of excitation received by a neuron. How do neurons adjust their responsiveness to avoid firing rates that are too high or too low? Here we provide evidence that ongoing activity can globally regulate the strength of excitatory synaptic connections onto cortical pyramidal neurons.

Whole-cell recordings were obtained from pyramidal neurons from cultures of P5-6 rat area 17 after 7-9 DIV, using an Axopatch 1D, in the presence of TTX and bicuculine. Miniature synaptic currents (minis) were recorded that could be blocked by the AMPA antagonist CNQX. Recordings were made from control cultures or sister cultures treated for 48 hours with TTX to block all spikes. In each of seven experiments, the quantal amplitudes from TTX treated cultures were larger than control cultures (32.8+1.1 pA, respectively; statistically significant difference, p,0.01, student's T test). Cumulative amplitude histograms from the two populations showed that the distribution was shifted to the right for the TTX-treated population (TTX-treated statistically different from control, Kolmagorow-Smirnof test, p,0.001). Treatment with bicuculine, which blocks inhibitory synaptic inputs and thus increases neuronal firing rates, produced a regulation of mini size in the other direction. Two days of bicuculine treatment reduced the average mini amplitude to 10.1 + 0.9pA, compared to control values of 16.5 $\pm$ 1.1 pA. No differences in resting potential, series resistances, whole cell capacitance, or rise times of minis were found for neurons maintained under these different conditions. This data indicates that the level of neuronal activity produces a long-lasting regulation in the quantal amplitude of AMPA-mediated synaptic transmission.

**Xiao-Jing Wang, Ph.D.**
Assistant Professor of Physics and
Volen National Center for Complex
Systems
Brandeis University
Waltham, Massachusetts

# Slowly Inactivating Potassium Currents and Cortical Dynamics

This talk discussed two types of electrical activities of cortical neurons: neuronal oscillations of the gamma (40 Hz), and theta (8 Hz) types, and spike adaptation and its functions in the real-time input-output computation of cortical neurons. Both topics are concerned with the main objective of Wang's research, namely to study how the behavior of neurons and neural networks is organized in time.

Brain rhythms are interesting because they are manifestations of synchronous activity of large neural populations, and because in principle they can carry temporal (phasic) information. We have been interested in the cellular and network mechanisms underlying the generation of various neural oscillations and the network synchronization. Recently, Wang proposed the first ionic conductance models for the neocortical fast (gamma, or 40 Hz) oscillations. The mechanism is based on a persistent sodium conductance and a slowly inactivating potassium conductance, which are located on the dendrite and are electronically separated from the spike generating sites near the soma. A similar mechanism may generate the theta rhythm in pacemaker neurons for the hippocampal theta wave. At the network level, Wang's team discovered that synaptic inhibition, not excitation, is often responsible for synchronizing large neural populations. They are currently pursuing detailed network modeling of these various neural waves, and of possible roles in the sequential coordination of behavior.

More recently, the team started to look at other forms of complex temporal dynamics of neurons and networks. One set of projects is to develop theoretical tools to analyze several very different time scales involved in a nervous system. Problems include the calcium dynamics of neurons and its control of the neural responses to time-varying inputs; variabilities in neural firing and neural coding of random inputs; and adaptation. Based on data from recent dendritic recording and calcium imaging experiments, and by computer simulations of a two-compartment conductance model, Wang's team investigated the interplay between voltage-dependent electrical activity and the intracellular calcium dynamics in cortical pyramidal neurons. A main characteristic of these cells is spike adaptation when subject to a constant stimulus. The time course of spike adaptation can often be approximated by a mono-exponential law, $f(t)=A+B*\exp(-t/\tau_{adap})$, where $f(t)$ is the instantaneous firing rate. By assuming that the spike adaptation is produced mainly by a calcium-dependent potassium conductance ($g_{AHP}$), Wang's team derives this exponential law semi-analytically, and relates the adaptation time constant ($\tau_{adap}$) with cellular parameters such as $g_{AHP}$ and the calcium decay time constant. By the same token, they introduce the notion of "calcium modes" when the calcium conductances are distributed over a multicompartmental dendrite.

The spike adaptation property endows the pyramidal neurons with interesting computational functions. With the team's model three phenomena are demonstrated here. (1) When the input consists of a periodic train of pulses, the response of the cell is sharply tuned to the lower input frequencies, similar to the observed contrast adaptation in the visual cortical neurons. (2) If an input is random and correlated in time, the signal is decorrelated in the cell's output ("efficient coding" and "novelty detection"). (3) In the presence of two or several inputs of slightly different amplitudes, the cell can selectively respond to the strongest input and suppress the others ("selective attention").

**Piali Sengupta, Ph.D.**
Assistant Professor of Neurobiology
and Volen National Center for
Complex Systems
Brandeis University
Waltham, Massachusetts

# Development and Function of Chemosensory Neurons in *C. elegans*

In vertebrates, the olfactory epithelium consists of thousands of similar types of sensory neurons, each uniquely identified by its sensory properties. This olfactory specificity is partly mediated by the expression of specific olfactory receptors in each neuron. Sengupta is interested in understanding the process by which each olfactory neuron acquires and regulates its characteristic properties.

The nematode *C. elegans* provides an excellent model system in which to study the development and function of chemosensory neurons. Worms respond to a large number of chemicals using approximately 32 chemosensory neurons. The functions of many of these chemosensory neurons have been defined by laser ablation experiments and mutants with defects in chemosensory responses have been identified. Several genes defined by these mutations have been cloned.

Using a behavioral screen, Sengupta and her team identified a gene *odr-7*, that encodes a member of the nuclear receptor family of transcriptional regulators (1). *odr-7* is expressed only in the AWA olfactory neurons. In *odr-7* mutants, the AWA neurons develop normally but lack all sensory function. Thus *odr-7* may regulate the expression of signaling molecules that provide AWA with its unique sensory profile.

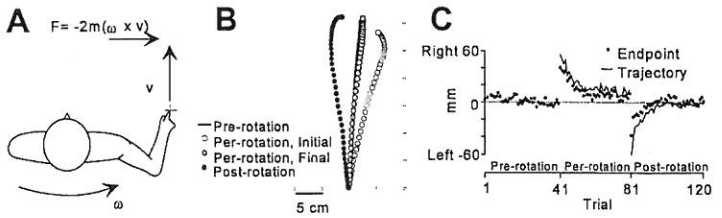
The team has recently shown that a target of *odr-7* regulation is the gene *odr-10* (2). *odr-10* encodes a seven transmembrane domain receptor for the volatile odorant diacetyl, sensed by the AWA neurons. *odr-10* mutants fail to respond selectively to diacetyl and the *odr-10* gene product is localized to the sensory cilia of the AWA neurons. Expression of *odr-10* under a heterologous promoter restores responses to diacetyl, but not to other odorants sensed by the AWA neurons. Sengupta plans to further examine the regulation of *odr-10* by *odr-7,* and to identify other genes that may also regulate *odr-10* expression and function. Additionally, Sengupta is examining how *odr-7* specifies AWA function, by identifying genes that act upstream and other genes downstream of *odr-7*.

In addition to *odr-10*, several large families of genes encoding putative chemosensory receptors in the worm have been identified (3). Analysis of the expression patterns of some of these genes has shown that these genes are expressed in small subsets of chemosensory neurons. Sengupta uses the candidate chemosensory receptor genes as markers to determine how the fates and functions of other chemosensory neurons in the worm are determined. Using genetic screens and behavioral assays, Sengupta will identify genes that are required for the development and function of these neurons, as defined by the expression of the appropriate receptor genes.

Sengupta is also interested in investigating the roles of nuclear receptors in the development of the worm sensory system. Although nuclear receptors have been implicated in pattern formation and tissue differentiation in many organisms, their roles in the development of the worm are largely unknown. She is exploring the possibility that *odr-7*-like genes function to specify other sensory cell types in the worm. Her team has identified several predicted genes that are homologous to *odr-7* in the worm genome sequence database (4). One of these genes, *nhr-22*, is expressed in multiple sensory neuron types. Sengupta is taking a reverse genetic approach to understand the roles of *nhr-22* and other *odr-7*-like genes in the development and function of chemosensory neurons in the worm.

**Paul DiZio, Ph.D.**
Assistant Professor of Psychology
and Volen National Center for
Complex Systems
Brandeis University
Waltham, Massachusetts

# Issues in Human Movement Control Raised by Studies in Unusual Force Environments




Over the past 30 years, equilibrium-point theories (Feldman, 1966, 1986; Bizzi, Polit & Morasso, 1976; Bizzi, Accornero, Chapple & Hogan, 1984) have become the predominant explanations for how descending neural commands regulate movement and posture, and the "perturbation paradigm" has emerged as a key method for testing them. Recently, James Lackner and Paul DiZio introduced a novel technique for perturbing movements that employs a rotating "artificial gravity" environment and obtained results that violate basic predictions of current theories.

Equilibrium-point theories state that commands issued to spinal neurons and interneurons directly regulate muscle length-tension relationships. According to this theory, movement is a mechanical consequence of attraction to an equilibrium posture at which muscles exert spring-like forces that balance opposing limb loads. If sufficient settling time is allowed, neither transient external loads imposed during a movement nor transient internal errors in the motor program will affect movement endpoint, which is a balance between only the final external forces and the final programmed length-tension relationships. Bizzi, Accornero, Chapple, and Hogan (1984) showed experimentally that the ability to move a manipulandum to targets is not altered by brief assistive or resistive perturbations applied through the manipulandum.

DiZio and his associates explored the effects of a novel sort of transient perturbation produced in a rotating room and found that movement endpoints and paths were deviated. Rotation provides one means of generating "artificial gravity" (centrifugal force) for long duration space missions and also produces Coriolis forces. They avoided the former by keeping experimental subjects at the axis of rotation and took advantage of the latter for perturbing movements. During rotation, transient Coriolis forces perpendicular to movement direction and proportional to velocity are generated, as illustrated in Figure A. Coriolis forces act without contacting the limb because they are inertial forces. By contrast, deviations produced with a manipulandum are always associated with spatially significant contact forces on the hand.

One experiment demonstrated that when subjects rotating at 10 rpm reach out to touch targets, they show substantial movement curvature and miss the desired target position by a large amount, both deviations being in the direction of the Coriolis force generated. Within about 10 movements, subjects adapt completely and move in straight paths to the target, without ever seeing their arm or feeling the targets (which are embedded in a smooth surface). When rotation ceases, subjects again make reaching errors with the adapted arm; endpoints and movement paths are initially deviated in the direction opposite the Coriolis force that had been present during rotation. Figures B and C illustrate the results.

Deviation of movement endpoints by Coriolis forces violates the fundamental prediction of equilibrium-point theories and excludes muscle length-tension characteristics from consideration as a neural control variable for motor programming. Rapid, complete adaptation to Coriolis force perturbations without vision means movement trajectories are closely monitored and controlled, on the basis of afferent signals from muscle spindles, joint receptors, and Golgi tendon organs in relation to efferent commands. The differences between results from these experiments with non-contacting Coriolis force perturations and results from previous experiments with mechanical perturbations applied through local contact indicate that cutaneous sensory signals also have a critical regulatory role in real-time trajectory control. Adaptation to Coriolis forces requires new motor commands to achieve the original trajectory, and the presence of mirror-image aftereffects reveals that these new commands produce forces that exactly cancel the Coriolis forces at every point in the movement trajectory, suggesting force as the controlled variable and a neural representation of limb dynamics as a mediator.