

Brandeis University

The Volen National Center for
Complex Systems

August 1999

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



The 1999 M.R. Bauer Foundation Colloquium Series, Distinguished Lecturer Series, and Scientific Retreat

Brandeis University

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

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Among the most important duties of an academic center are the dissemination of emerging information and the creation of a forum to discuss new ideas. With the generous support of the M.R. Bauer Foundation, now in its fifth year, the Volen Center for Complex Systems has again mounted an impressive series of colloquia on emerging topics in neuroscience as well as a scientific retreat highlighting the work of outstanding graduate students in neuroscience. An exciting new enterprise this year has been the M.R. Bauer Distinguished Guest Lecturer Series. I am very pleased to present the following proceedings, which reflect the results of this year's undertakings and help to advance the Volen Center's core mission.

In 1998-99 the M.R. Bauer Foundation Colloquium Series featured talks that elucidate a wide range of fascinating topics, including the uniqueness of episodic memory, the role of zinc in neuronal death, and the hippocampus minor as an example of the historic role of neuroanatomy in the debate on evolution. As in past years, our speakers comprised a selection of the most distinguished neuroscientists active today, including Dennis Choi of Washington University School of Medicine, Charles G. Gross of Princeton University, Richard W. Tsien of Stanford University of Medicine, Michael Gazzaniga of Dartmouth College, and Endel Tulving of the University of Toronto. Together, the speakers offered valuable insights into developments in their chosen areas of research and served to broaden and deepen the ongoing investigation of neuroscience ranging from molecules to cognition at Brandeis University.

A highlight of the year has been the new M.R. Bauer Distinguished Guest Lecturer Series. This new program brought to campus two of the most outstanding neuroscientists in the

world—Dr. Zach Hall, Vice Chancellor of the University of California, San Francisco, and Dr. Bert Sakmann, chair of the Department of Cell Physiology at the Max Planck Institute for Medical Research in Heidelberg, Germany. Dr. Hall, who has made fundamental contributions to understanding the neuromuscular junction, recently served as director of the National Institute of Neurological Disorders and Stroke, one of the National Institutes of Health. His perspective on the creation of national science policy was highly informative. Dr. Sakmann, who shared the Nobel Prize for Physiology and Medicine in 1991 for his discoveries concerning single ion channels, spoke about his active research program. He described his efforts to address the basic mechanisms underlying higher brain functions. Both M.R. Bauer Distinguished Guest Lecturers presented public talks, gave classroom lectures, visited many of the Volen Center's laboratories, made presentations at the Neuroscience Journal Club, and interacted with members of the Brandeis science community, including faculty, postdoctoral researchers, graduate students, and undergraduate students. The two visitors brought valuable insights to our faculty and students.

Sponsored by the M.R. Bauer Foundation, the 1999 Volen Retreat was held at the Marine Biological Laboratory in Woods Hole, Massachusetts, on February 23 and 24. In distinction to previous years, when faculty and postdoctoral fellows were the focus of the Retreat, this year's event featured former and current graduate students from the Volen Center. The graduate students presented their work, ranging from studies of artificial intelligence, neural development, and biological clocks to ion channel properties, learning, and memory. I was especially pleased by the scope and quality of their

research, which underscore the Volen Center's excellence in training and education. The Retreat's keynote speakers were Emilio Salinas of the National Autonoma University of Mexico, who spoke on "Stimulus encoding during somatosensory discrimination: spike timing, firing rate and signal-to-noise modulations," and Hongkui Zeng of MIT's Center for Learning and Memory and Center for Cancer Research, who spoke about "Hippocampus-dependent learning in conditional transgenic mice." Approximately 125 scientists and students attended the annual two-day event. The retreat offers an excellent opportunity each year for scientists at the Volen Center to learn more about each other's work and to benefit from the suggestions and perspectives of colleagues. It is also a marvelous opportunity for younger scientists, at the graduate and postdoctoral level, to gain professional exposure, establish new ties, and learn from the insights and critiques of older scientists. These young neuroscientists represent future generations of researchers and teachers who will carry the study of the brain far beyond what we envision now.

The publication of these proceedings is a major element in the Volen Center's effort to encourage scientific collaboration and discussion. The M.R. Bauer Foundation Colloquium Series and Scientific Retreat have proven to be highly successful in bringing together the neuroscience community at Brandeis and more broadly in North America, in fostering the exchange of ideas and methods across disciplinary boundaries, and in advancing the study of learning, memory, and cognition. I am pleased to thank the M.R. Bauer Foundation for underwriting these important activities.

Laurence F. Abbott
Nancy Lurie Marks Professor of Neuroscience and Director, Volen National Center for Complex Systems

Richard W. Tsien, Ph.D.

Professor of Biology
Stanford University
Stanford, California
October 2, 1998

Novel Forms of Activity-Dependent Signaling at CNS Synapses Involving Specific Calcium Channels

Plasticity, the modulation of activity as a result of experience, is a fundamental feature of brain function. It is manifested at many levels of organization, including behavior of the organism, output of large neural networks, and properties of individual nerve cells and of the synaptic connections among them. The molecular mechanisms involved in synaptic plasticity have been widely studied in recent years, and this has emerged as one of the most active and exciting areas of research in modern cellular neurobiology. Although diverse molecular pathways have been implicated in synaptic plasticity, one common theme that has emerged is that calcium plays a central role.

Calcium can enter neurons in a variety of pathways, including several kinds of calcium channels and some ligand-gated ion channels. The Tsien laboratory has been in the forefront of studies of calcium for many years, and has played a key role in defining calcium channel diversity. A major challenge for neurobiologists is to define the roles these different calcium entry pathways play in neuronal physiology. More specifically, the role of different modes of calcium entry in synaptic transmission and synaptic plasticity is of great interest. Tsien showed in his lecture that calcium entry through one kind of calcium channel evokes vesicle fusion at the presynaptic membrane and release of

neurotransmitter into the synaptic cleft. Entry via another kind of calcium channel does not appear to evoke neurotransmitter release, but instead signals to the cell nucleus. A complex cascade leads to the calcium-dependent phosphorylation of the transcription factor CREB. As a result of calcium entry, the ubiquitous calcium-binding protein calmodulin is translocated in the nucleus, where it activates a particular kind of calcium/calmodulin dependent protein kinase. It is this enzyme that in turn phosphorylates CREB, and allows CREB to activate the transcription of a number of different proteins. These proteins then are able to influence the properties of the synapse over a long period of time. The results described in this lecture emphasize the richness and complexity of the signaling pathways that can influence neuronal function.

Charles C. Gross, Ph.D.

Professor of Psychology
Princeton University
Princeton, New Jersey
November 2, 1998

The Hippocampus Minor and Man's Place in Nature: A Case Study in the Social Construction of Neuroanatomy

In mid nineteenth century Britain the possibility of evolution and particularly the evolution of man from apes was vigorously contested. Among the leading anti-evolutionists was the celebrated anatomist and paleontologist Sir Richard Owen, and among the leading defenders of evolution was T. H. Huxley.

In his argument against the evolution of humans from apes and, more generally, against the possibility of organic evolution, Owen claimed that the human brain was fundamentally different from that of the ape brain and therefore the transmutation of one species into the other was impossible. The uniqueness of the human brain, he claimed, was that only it had a "hippocampus minor." This structure, today termed the "calcar avis" is in fact, a rather small indentation in the wall of the lateral ventricle of the brain.

Huxley set out on a systematic campaign to disprove Owen's claim of the uniqueness of the human brain. His purpose was not merely to correct Owen's supposed anatomical error, but to portray him as dishonest and incompetent and therefore to eliminate him as a credible critic of Darwin's theory of evolution. Huxley and his allies proceeded to demonstrate (and exaggerate) the existence of a hippocampus minor in a great variety of primate species. In the course of his anatomical studies Huxley discovered and named the

calcarine sulcus. The controversy over the hippocampus minor evoked widespread interest in the lay media. Huxley used it to help transfer power from the dominant Oxbridge clergyman-naturalists to the new professional scientists, at the center of which were Huxley and his allies.

At this time little was known about the functions of the brain structure. Owen's stress on the importance of ventricular anatomy derived from the central position of the brain ventricles in Galen's system of physiology that had dominated physiology and medicine from the second century into the 19th.

This tale illustrates both the extraordinary persistence of ideas in biology and the role of the political and social matrix of science. It also exemplifies the continuing attempt of humans to differentiate themselves from the rest of the animal kingdom.

Dennis W. Choi, Ph.D.

Professor of Neurology
Washington University
School of Medicine
St. Louis, Missouri
February 5, 1999

Zinc and Ischemic Neuronal Death

The metal zinc is an essential dietary nutrient, present as a component of many proteins in all the cells of our bodies. Zinc aids the function of many enzymes, and helps regulate the use of genes as templates for making new proteins. It also has a special function as a signaling substance—a neurotransmitter—in the central nervous system. It is stored within nerve endings, and released to the space outside nerve cells during nervous system activity, together with other neurotransmitter substances, in particular glutamate. The normal functional effects of zinc are mediated in large part by its ability to alter the behavior of certain glutamate receptors, receptor proteins on the surface of the membrane of the nerve cells that recognize glutamate and consequently cause the nerve cell to become electrically active.

Despite this important normal function of zinc, recent studies have suggested that zinc may also be a key mediator of the nerve cell death associated with several types of disease conditions, including temporary loss of blood flow as occurs during a cardiac arrest (heart stoppage) followed by resuscitation. If loss of blood flow lasts longer than several minutes, brain damage can result, even if all other organs return to normal function. This brain damage typically causes memory disturbances and other difficulties, or even coma if severe enough.

Certain brain neurons are known to be especially susceptible to death induced by transient loss of blood flow. My colleagues and I have modeled this process of neuronal death by transiently reducing brain blood flow in rats for 10 minutes. Although brain blood flow was completely restored after this 10-minute deprivation period, certain selectivity vulnerable brain nerve cells went on to die over the next one to three days, just as after cardiac arrest in humans. These selectivity vulnerable rat nerve cells contained notably large quantities of zinc. To test the idea that excessive zinc entry into the cells caused their death, we injected a blockage substance, calcium-EDTA, into the ventricles (fluid-filled spaces) of the rat brains. The calcium-EDTA trapped the zinc released from nerve endings before it could enter the cells; as a result many fewer nerve cells filled with zinc and went on to die.

Our results suggest that brain zinc stores, while presumably useful for normal brain function, might also have a dangerous side, becoming killers of nerve cells after a transient lowering in blood flow. We are presently performing studies to determine exactly how excessive amounts of zinc entry may kill nerve cells. We hope that strategies designed to interfere with zinc entry into nerve cells, or the specific consequences of that entry for nerve cell metabolism, may lead to the development of novel treatments which might be used in the future to reduce brain damage in patients suffering from cardiac arrest.

Michael S. Gazzaniga

Professor of Psychology
Center for Cognitive Neuroscience
Dartmouth College
Hanover, New Hampshire
March 15, 1999

Consciousness and the Brain

My thinking about the question of consciousness started early—since the afternoon in Roger Sperry's lab at Caltech almost 40 years ago when I tested the first split-brain patient. Right off the bat it seemed that whatever consciousness was, one could have two of them after the neurons which connected the two cerebral hemispheres were surgically separated. Mind left did not appear to know about mind right, and vice versa. Those first impressions, while factually enduring, left much to be desired as a sophisticated perspective on the question of consciousness. My situation echoed Tom Wolfe's admonition: practice writing for 20 years before you seek a publisher.

Classic split-brain work has highlighted how the left and right brain each possesses its own particular functions. The studies would lead one to believe that the brain is a collection of modules. Thus, the left hemisphere is specialized for not only language and speech, but also for intelligent behavior. After human cerebral hemispheres are disconnected, a patient's verbal IQ remains intact, and his problem-solving capacity, as observed in hypothesis formation tasks, remains unchanged for the left hemisphere. The left hemisphere thus remains unchanged from its pre-surgical capacity; yet the largely disconnected, same-size right hemisphere becomes seriously impoverished in many cognitive tasks. While the largely isolated right hemisphere remains superior to the

isolated left hemisphere in certain activities—such as recognizing upright faces, having better attentional skills, and perhaps also expressing more emotions—it is poor at problem solving and numerous other mental activities. Thus, the left has modules specialized for higher cognitive function while the right has modules specialized for other functions.

Visuo-spatial function, for example, is generally more acute in the right hemisphere, but left-hemisphere integration may be needed to perform higher-order tasks. The use of tactile information to build spatial representations of abstract shapes appears to be better developed in the right hemisphere; however, tasks such as the Block Design test from the WAIS, which are typically associated with the right parietal lobe, appear to require integration between the hemispheres in some patients. Furthermore, even though the right hemisphere is better able to analyze unfamiliar facial information than is the left hemisphere and the left is better able to generate voluntary facial expressions, both hemispheres are capable of facial expression when spontaneous emotions are expressed.

The uniquely human skills we possess may well be produced by minute and circumscribed neuronal networks sometimes referred to as "modules." And yet our highly modularized brain generates a feeling in all of us that we are integrated and unified. How does that feeling come about, even though we are a collection of specialized modules? The answer appears to be that there is a specialized left hemisphere system we have designated as the "interpreter," a device that seeks explanations for

why events occur. The advantage of having such a system is obvious. By going beyond observing contiguous events and asking why they happened, a brain can cope with these same events more effectively, should they happen again. Recent investigations of ours have extended research on the properties of the interpreter and how its presence influences other mental skills. There are, for example, hemisphere-specific changes in the accuracy of memory processes. The predilection of the left hemisphere to interpret events has an impact on the accuracy of memory. When subjects were presented with pictures that represented common events (i.e., getting up in the morning or making cookies) and then several hours later were asked to identify whether pictures in another series appeared in the first, both hemispheres were equally accurate in recognizing the previously viewed pictures and rejecting the unrelated ones. Only the right hemisphere, though, correctly rejected pictures in the second set that were not previously viewed but were related to pictures from the first. The left hemisphere incorrectly "recalled" significantly more of these pictures as having occurred in the first set, presumably because they fit into the schema it had constructed regarding the event. This finding is consistent with the view of a left hemisphere "interpreter" that constructs theories to assimilate perceived information into a comprehensible whole. In doing so, however, the elaborative processing has a deleterious effect on the accuracy of perceptual recognition. This result has been extended to include verbal material.

By emphasizing specialized circuits that arise from natural selection, we see that the brain is not a unified neural net that supports a general problem solving device. If we accept this notion, we can concentrate on the possibility that smaller, more manageable circuits produce awareness of a species' capacities. Holding fast to the notion of a unified neural net means we can understand human conscious experience only by figuring out the interactions of billions of neurons. That task is hopeless. My scheme is not.

The same split-brain research that exposed shocking differences between the two hemispheres also revealed that the human left hemisphere has the interpreter. The left brain interpreter's job is to interpret our behavior and responses, whether cognitive or emotional, to environmental challenges. The interpreter constantly establishes a running narrative of our actions, emotions, thoughts, and dreams. It is the glue that keeps our story unified and creates our sense of being a coherent, rational agent. It brings to our bag of individual instincts the illusion that we are something other than what we are. It builds our theories about our own life, and these narratives of our past behavior seep into our awareness.

The problem of consciousness, then, is tractable. We do not have to find the code of one huge, interacting neural network. Instead, we must find the common and perhaps simple neural circuit(s) that enables vertebrates to be aware of their species-specific capacities, and the problem is solved. The same enabling circuit(s) in the rat is most likely present in the human brain, and understanding that point makes the problem scientifically tractable. What makes us so grand is that the circuit has so much more to work with in the human brain.

Our brains are automatic because physical tissue carries out what we do. How could it be any other way? That means they do it before our conceptual self knows about it. But the conceptual self grows and grows and reaches proportions that find the biologic fact that our brain does things before we are consciously aware of them of interest but not disheartening. The interpretation of things past has liberated us from a sense of being tied to the demands of the environment, and it has created the wonderful sense that our self is in charge of our destiny. All of our everyday success at reasoning through life's data convinces us of our centrality. Because of that we can drive our automatic brains to greater accomplishment and enjoyment of life.

Endel Tulving, Ph.D.

Professor of Psychology
Rotman Research Institute
University of Toronto
Toronto, Canada
April 12, 1999

What is Episodic Memory and Why is it Unique?

There are many different types of memory one can talk about. One of the main distinctions is between semantic and episodic memory. With episodic memory, the subject not only has the memory, but can remember something about the setting in which the remembered information was learned. Conversely, with semantic memory, the subject cannot recall the context of the initial learning.

The nature of episodic memory, however, is far more complex. It specifically has to do with the ability for a person to travel back in time to re-experience remembered events. In this way, episodic memory links experience of the past, present, and future. The term autonoetic (from the Greek word Gnosis) consciousness—awareness of subjective experiences in the past, present, and future. Autonoetic consciousness is a special feature of episodic memory; the different types of consciousness associated with semantic memory and procedural memory are termed noetic (knowing) and anoetic (without knowledge) respectively.

Experimentally, one can ask subjects whether they “remember” something or “know” it, thereby distinguishing between autonoetic and noetic (i.e., without the re-experiencing of the event) awareness. The brain regions involved, as well as electrophysiological features, depend upon whether the memory was rated as “remembered” or “known.” Such studies suggest that the prefrontal and hippocampal brain regions are involved in autonoetic awareness.

These results are consistent with the HERA model, which implicates left prefrontal cortex for semantic retrieval and right prefrontal cortex for episodic retrieval.

A recent lesion patient, M.L., provides additional support for this approach to the unique nature of episodic memory. M.L. has damage to part of the right frontal cortex, and consistent indeed, has an impaired capacity to perform episodic memory tasks (as assessed by the remember/know paradigm).

Introduction

A highlight of the year has been the new M.R. Bauer Distinguished Guest Lecturer Series. This new program brought to campus two of the most outstanding neuroscientists in the world—Zach Hall, vice chancellor of the University of California, San Francisco, and Bert Sakmann, chair of the Department of Cell Physiology at the Max Planck Institute for Medical Research in Heidelberg, Germany.

Both guests visited Brandeis for a full week. They each gave a public talk (summarized on the following pages), spoke to classes, met formally with graduate students and postdoctoral fellows, presented at journal clubs, and met with many of the neuroscience laboratories. Their schedules were quite full, very educational, and enjoyed by all!

Zach W. Hall, Ph.D.

Vice Chancellor for Research
University of California
San Francisco, California
February 1, 1999

“Science and Government: A California Cracker Goes to King Harolde’s Court”

Based on my experience for three years as director of the National Institute of Neurological Disorders and Stroke, following a conventional academic career as professor and chairman of the Department of Physiology at the University of California, San Francisco, I make a number of observations about the relation between science, politics, and public policy. The intent of these observations is to help bridge the gap of understanding and culture that separates the world of academic science and that of national biomedical science administration, as represented by the National Institute of Health (NIH), the leading biomedical research institution in the world. My observations are also meant to underline several tensions or larger questions that modern biomedical science faces as it progresses into the 21st century.

Four major themes were discussed. The first (“Insiders vs. Outsiders”) points to the need for a healthy exchange of personnel and ideas between NIH and the extramural world of biomedical research. The Intramural Research Program of the NIH was used as an example of the problems that can occur when such exchange is sub-optimal. A system of largely internal hiring that worked well when the NIH was at the pinnacle of research excellence in the late sixties and early seventies resulted in an institution with large pockets of stagnation 25 years later. The Marks-Cassell report and its vigorous implementation under the direction of

Dr. Harold Varmus has now resulted in important changes in hiring policies for scientists that should restore the NIH to its previous excellence.

A second theme ("Directed vs. Undirected Research") examined a series of questions dealing with the way science is performed (curiosity-driven vs. mission driven); the way in which it is organized (big science vs. small science); the way it is funded and directed ("bottom-up vs. top down"). Curiosity-driven science is most familiar and comfortable for basic scientists, who often work in relatively small groups, whereas for clinical scientists, often concerned with a particular disease, science is mission-driven, and often done by teams of investigators. Both are needed and each group needs to understand the other. Centrally directed and organized scientific initiatives are likely to increase as technology makes "big science" possible.

The third theme ("Doing Science vs. Curing Disease") dealt with the discrepancy between the goals of many scientists, particularly basic scientists, and that of Congress. Congress's interest, curing disease, is unequivocal and clear. The goal for basic scientists should not be to try to interest the Congress in the importance of science for the purpose of understanding, but to show its utility and necessity for curing disease. Because members of the Congress have varying

sophistication about science and how it is carried out and because the membership changes every two years, information and education of public officials by scientists on these points is an important and continuing need.

Finally, ("Political Advocacy") patient advocacy groups are among the most important lobbyists in Washington for biomedical research. They bring to the Congress the personal dimension of disease research and a sense of focus and zeal. Although scientists agree with the advocacy groups on the ultimate aims of research, they often differ on how to get there. Patient advocacy groups are intensely focused on a single disease or group of diseases, are interested in short-term results, and are often competitive with each other for the science dollar. Increased understanding and continuing education are essential to a strong working relationship with these groups. In advocacy, both for specific causes, and for the larger enterprise of biomedical research, we must emphasize the possibilities offered by science, but must do so responsibly and realistically.

Coincidence Detection in Cortical Cells

Coincidence Detection in Cortical Cells addresses an issue that is part of the more basic problem of how the environment is represented in the brain such that an organism can respond in an appropriate manner when the environment changes. In other words, what are possible cellular and molecular mechanisms that underlie those brain functions, that are sometimes referred to as "higher" brain functions, such as recognition of an object, learning, and retrieval from memory?

The underlying assumption we make in trying to understand such functions is that the brain operates by electrical signals generated by the constituting nerve cells. An external stimulus, say a visual scene and its different features, is encoded by a sequence of action potentials in ensembles of neurons in the six cortical layers. If we want to understand brain functions mechanistically we have to be able to monitor the ever-changing pattern of electrical signals in neuronal ensembles. This means to find out how the complex pattern of signals in the so-called "representational" cortical fields is generated and how the stimulus is "encoded" by the ever changing pattern of electrical signals. There are several views on how this may happen.

One view is referred to as "Rate coding" the other one as "Temporal coding." Both types of stimulus representation require an ensemble of "read-out" neurons. These must be sensitive to the temporal structure of the electrical activity of those cortical

neurons that are lower in the hierarchical order. For example they must be sensitive to synchronous activity of the lower-order neurons. Possible mechanisms of coincidence detection are found in the large neurons of cortical layer 5 which are the cortex' main read-out neurons. Multiple simultaneous recordings from different compartments of single L5 neurons suggested that at threshold synaptic stimulation sodium dependent action potentials are initiated in the axon which propagate actively in two directions—orthogradely into the axonal arbor and retrogradely into the dendritic arbor. With stronger stimulation an additional action potential initiation zone in the distal apical dendrite is operating. In this dendritic zone, calcium dependent action potentials are initiated that spread along the dendrite to the axonal initiation region to influence the output discharge pattern of the neuron in a specific way. Thus the L5 pyramidal neurons of the neocortex have two action potential initiation zones. They can interact in such a way that synaptic input to the basal dendrites from layer 5, when occurring almost coincident (within a few milliseconds) with synaptic input to the apical tuft from layer 1 will generate a high frequency burst of several action potentials.

The intracortical innervation pattern of L5 pyramidal neurons is such that the generation of burst firing by coincident synaptic inputs to the basal and apical dendrites respectively would be a mechanism to associate local, columnar synaptic input to the *basal* dendrites arriving from a primary sensory area with an input to the *apical* tuft dendrites arriving from secondary sensory areas.

Furthermore, synchronized burst activity of connected cortical neurons can change the strength of their synaptic connections. Coincident input dependent burst activity can represent one mechanism that initiates long-term changes in the synaptic efficacy of wiring of cortical neurons. In summary, one could speculate that the generation of bursts of action potentials in layer 5 of the cortex signals to other parts of the brain that coincident activity in two sensory areas, say the visual and somatosensory areas, has occurred. If this happens repeatedly the connection between the bursting neurons would be strengthened leading to a lower threshold for the reaction of the organism to a specific set of external stimuli.

The 1999 Volen National Center for Complex Systems Scientific Retreat

On February 23 and 24, 1999, the Volen National Center for Complex Systems held its 11th annual scientific retreat. This year's retreat highlighted the excellent work done by our life science graduate students. On Thursday evening the two keynote speakers were former graduate students, both of whom have gone on to further their careers at other universities. On Friday, eight lecturers were current graduate students. They made terrific presentations highlighting the high caliber of students and research taking place within the Center.

Approximately 125 people attended this year's retreat, which was held once again 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 (faculty, postdocs, and students) together off-campus for a 24-hour retreat was again tremendously successful. The MBL provides a stimulating environment for interactions as well as a scenic site for walking and relaxing.

The Center for Complex Systems

Marine Biological Laboratory
Woods Hole, Massachusetts
February 23-24, 1999

Tuesday, February 23, 1999

2:00 pm

Arrival and check-in

4:30 pm

Poster session and refreshments

6:00 pm

Dinner

Former Center for Complex Systems Graduate Students

7:00 pm

Emilio Salinas, Ph.D.
Instituto de Fisiologia Celular
Universidad Nacional Autonoma de Mexico

"Stimulus Encoding During
Somatosensory Discrimination:
Spike Timing, Firing Rate and
Signal-to-Noise Modulations"

7:45 pm

Hongkui Zeng, Ph.D.
Center for Learning and Memory
Center for Cancer Research
Massachusetts Institute of
Technology
Cambridge, Massachusetts
"Hippocampus-dependent Learning
in Conditional Transgenic Mice"

9:00 pm

Music and dancing

Wednesday, February 24, 1999

7:00-8:30 am

Breakfast

Volen Center for Complex Systems Graduate Students

Brandeis University
Waltham, Massachusetts

8:30 am

Meredith LeMasurier, Ph.D. Student
with Professor of Biochemistry Chris
Miller
"Conductance Properties of the KcsA
K⁺ Channel from *Streptomyces*
Lividans"

8:50 am

Frances Chance, Ph.D. student with
Professor of Biology Larry Abbott
"A Mode of Direction Selective Visual
Responses"

9:10 am

Tim Strassmaier, Ph.D. student with
Professor of Biochemistry Dan Oprian
"Peptide-based Inhibitors of HIV-1
Mediated Membrane Fusion"

9:30 am

Andy Garland, Ph.D. student with
Professor of Computer Science Rick
Alterman
"Multiagent Learning Despite Limited
Communication"

10:00 am

Break

10:30 am

Trina Sarafi, Ph.D. student with
Assistant Professor of Biology Piali
Sengupta
"Development Specification of
C.elegans Chemosensory Neurons"

10:50 am

Jessica Pisano, Ph.D. student with
Assistant Professor of Biology Susan
Birren
"Developmental Divergence of the
Enteric and Sympathetic Nervous
Systems"

Emilio Salinas, Ph.D.

Instituto de Fisiología Celular
Universidad Nacional Autónoma de
Mexico

February 23, 1999

Stimulus Encoding During Somatosensory Discrimination: Spike Timing, Firing Rate and Signal-to-Noise Modulations

The sensation of flutter is felt when mechanical vibrations between 5-50 Hz are applied to the skin. Some primary somatosensory neurons are driven very effectively by periodic flutter stimuli; their evoked spike trains typically have a periodic structure, with highly regular time differences between spikes. It has been strongly argued that these time intervals may underlie a subject's capacity to discriminate flutter frequencies. Is it true that periodicity in cortical spikes plays a functional role? Do cortical somatosensory neurons exploit such a temporal code? We investigated these hypotheses by analyzing extracellular recordings from primary (S1) and secondary (S2) somatosensory cortices of monkeys trained to perform a frequency discrimination task.

The analysis was based on Shannon's mutual information, which is a powerful statistic that measures the strength of association between two variables. We found that the information about stimulus frequency carried by the periodic spike intervals was indeed extremely high in S1 but decreased dramatically in S2, whereas the information provided by the mean rate was moderate but similar across areas. Many S2 neurons sustained their responses for a few hundred milliseconds after stimulus offset, during an inter-stimulus period in which the monkey needs to remember the stimulus frequency. The information provided by the firing rate during this period was still substantial, but the information from spike periodicity was practically extinguished. Additionally, the firing rate also conveyed

11:10 am

Maki Kaneko, Ph.D. student with
Professor of Biology Jeff Hall
"Clock cells in the Fruit Fly *Drosophila*
Revealed by Clock-gene Expression"

11:30 am

Jeremy Caplan, Ph.D. student with
Assistant Professor of Psychology
Michael Kahana
"Human Theta: Probing the Cortical
Surface"

12:00 pm

Lunch

1:00 pm

Departure

Hongkui Zheng, Ph.D.

Center for Learning and Memory
Center for Cancer Research
Massachusetts Institute of Technology
Cambridge, Massachusetts
February 23, 1999

Study of Hippocampal Memory Mechanisms in Conditional Knockout and Transgenic Mice

information about average frequency during discrimination based on periodic vibrations—by design, information from spike timing is practically eliminated with these stimuli. Finally, only the firing rate signal was enhanced by the behavioral significance of the stimuli.

Hence, we conclude that the neural code for flutter frequency is probably based on firing rate; the exquisite timing of stimulus-driven spikes in S1 seems unrelated to it. These results attach a cautionary note to studies in which functional relationships are inferred exclusively from observed correlations between neuronal firing and variations in stimulus or behavior: some neuronal response attributes may covary greatly and accurately with physical quantities without necessarily having any meaning in the language of neuronal interactions.

The neural mechanisms underlying learning and memory have been proposed at the synaptic level and the network level. Synaptic plasticity (such as long-term potentiation and long-term depression) can be a way of encoding memory information through long-lasting modification of the strength of a specific set of synaptic connections. Coordinated oscillatory activities in the neural network may provide a spatial and temporal framework for the memory information to be stored and transferred in different brain regions. The hippocampus has been the prototypic model system for the study of memory mechanisms.

The Ca^{2+} /CaM-dependent protein phosphatase calcineurin is suggested to be involved in certain types of synaptic plasticity, such as LTD. But the exact role of calcineurin in plasticity has been elusive due to the lack of cell- typespecific manipulation in previous studies. I have generated a line of mice in which the calcineurin gene is specifically knocked out in the pyramidal neurons of the CA1 region in the hippocampus. The role of calcineurin in synaptic plasticity will be examined in the Schaffer collateral—CA1 pathway where the gene is only missing in the postsynaptic cells. The unique contribution of CA1 plasticity to memory will also be assessed by behavioral learning tasks and in vivo recording of CA1 place cell activities in these mutant mice.

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Conduction Properties of the KCSA Channel from *S. Lividans*

The inhibitory interneurons in the hippocampus have very different properties from the excitatory principal neurons. Although a minor population, ~10 percent of total neurons, they are believed to play critical roles in shaping the activities of excitatory neurons through feed forward and feedback inhibition, and in generation of various rhythmic activities. Due to their extreme anatomical and physiological diversities, the functions carried out by interneurons are probably also very diverse. Therefore it has been difficult to study using conventional methods which lack cell-type specificity. I am trying to develop interneuron subtype-specific transgenic lines of mice. These lines will be used for genetic manipulations in one type of interneurons at a time, to dissect out interneurons' function in memory.

Ion channels are integral to many biological processes including cell volume regulation, muscle contraction, and the transmission of nerve impulses. We are interested in ion channel function at the molecular level, how the channel catalyzes the movement of ions across the cellular membranes. Last year the first high resolution crystal structures of a potassium channel, that of the KcsA K⁺ channel from *Streptomyces lividans*, were solved (Dyle et al, *Science* (1998) 280: 69-77). This structure represents a large step forward towards the goal of understanding the molecular mechanisms of K⁺ channels.

Although the eukaryotic K⁺ channels have been extensively studied, little is known about the K⁺ conduction properties of KcsA. The focus of these studies has been on examining K⁺ conduction through KscA. We have adapted a planar bilayer system for the reconstitution and high-resolution recordings of single KcsA channels. The basic properties of this channel were studied, including how the potassium current varies with voltage across the bilayer. The single-channel current-voltage relationship rectifies, with larger conductances at negative voltages than at positive voltages.

Additionally, at positive potentials KcsA exhibits a flickery behavior in the open state that is not observed in negative potentials. We have also examined how the potassium currents through KcsA for K⁺ over other monovalent ions. We have found that KcsA resembles eukaryotic potassium channels on a gross level, but it is unique in some finer details which are being examined in greater detail.

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A Model of Direction Selective Visual Responses Based on Synaptic Depression

Neurons in the primary visual cortex can demonstrate direction-selectivity, exhibiting strong responses to images moving in one direction and weak responses to images moving in the opposite direction. Recently, experimental work on brain slices led to a descriptive model of synaptic depression, a form of synaptic plasticity in which the strength of a synapse becomes progressively weaker with repeated stimulation. We examine the effect of synaptic depression on neuronal responses by introducing this descriptive model of synaptic depression into a model of a basic primary visual cortical circuit. Direction-selectivity can arise in the model if two distinct sets of inputs, with receptive fields that are spatially shifted from each other, arrive separately through depressing and non-depressing synapses. The model can account for data on direction-selective cells over a wide range of conditions.

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Peptide-based Inhibitors of HIV-1 Mediated Membrane Fusion

The core of the human immunodeficiency virus (HIV) is encapsulated in a lipid membrane. In order for the viral core to gain access to a cell's interior—the first step in infection—the viral membrane must fuse with the cellular membrane. The viral glycoproteins gp120 and gp41 associated with the viral membrane are responsible for binding to specific cellular receptors and mediating fusion of the viral and cellular membranes. We have implemented a cell-cell fusion assay to measure the membrane fusion activity of HIV-1 gp120/gp41. The cell-cell fusion assay was used to test the efficacy of hybrids between gp41 derived peptides and organic segments, identified from a combinatorial chemical library designed to yield small organic molecules capable of substituting for a portion of the gp41 peptide by binding to a particular cleft on gp41. Peptides, which bind to this cleft on gp41, are potent inhibitors of HIV membrane fusion. Small molecules that bind to this same cleft on gp41 could be lead compounds for the development of a new class of anti-HIV drugs. The peptide/organic hybrid inhibited HIV membrane fusion in the cell—cell fusion assay. The concentration of peptide/organic hybrid required to reduce the fusion activity by 50 percent, the EC₅₀, was approximately tenfold lower than for the peptide alone. Further work will be required to identify organic compounds that can fully substitute for the peptide as inhibitors of HIV mediated membrane fusion.

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Multiagent Learning Despite Limited Communication

Traditional techniques in artificial intelligence reflect the fact that early models of behavior assumed actors were isolated thinkers. These techniques have needed to be refined or replaced as research focus has shifted towards groups of collaborating agents who coordinate their efforts via communication. An important consideration for a collaborative model is that communication meant to prevent unnecessary action effort can take longer than the unneeded actions would have; in the worst case, a near-constant stream of lengthy conversations can effectively preclude any action. The work described in this talk extends traditional techniques in two important ways. First, an activity model is developed that reduces the amount of information exchanged and the frequency that communication occurs. Second, agents are equipped with a memory-based learning framework that allows the agents, over time, to better coordinate despite limited communication. A central feature of the learning technique is that agents independently learn by analyzing their run-time behavior. Empirical results from an implemented test-bed verify the efficacy of the technology developed.

An important issue that distinguishes a multiagent system from a traditional (single agent) one is determining how the group of agents will coordinate their activities. Early multiagent planners made sure that agents were properly coordinated by either having a centralized planner assigning plans to the agents or by having the agents

exchange plan structures during planning. In either case, the plans were generated and the execution was assumed. In current research on autonomous agents, where run-time conditions are assumed to be uncertain and dynamic rather than pre-determinable and static, a model of behavior that depends on the creation of an overarching plan at the outset of a cooperative activity becomes problematic.

Over the last decade, sound theoretical frameworks have been developed that specify exactly what information needs to be communicated during the course of joint activities in order to maintain coordination at all times. Although these models "guarantee" coordination, the communication costs they entail are potentially impractical for dynamic environments. A critical issue, therefore, is developing a multiagent system that allows multiple agents to remain coordinated, while keeping communication costs manageable.

Learning in a dynamic, uncertain, multiagent setting is a challenging task. Our learning techniques are motivated by the theory that the development of distributed cooperative behavior in people is shaped by the accumulated cultural-historical knowledge of the community. An agent's memory contains the breadth of knowledge acquired through interacting with other agents and the world during the course of solving problems. The cornerstone of the memory-based learning framework of the agents are case-based reasoning techniques to convert noisy run-time activity into procedures useful for future problem-

solving activities. The coordinated procedures created by this conversion process are stored into memory by each agent independently. Analyzing run-time performance, rather than planner performance, enables agents to learn procedures beyond the scope of their first-principles planner rather than to simply cache previously known ones.

The models of behavior and learning described above have been implemented into a test-bed system, composed of over 25,000 lines of source code. Empirical studies verify that communicating only coordination points is advantageous when communication costs are high and that our learning techniques are effective at reducing the run-time effort expended by the community of agents to solve problems.

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Developmental Specification of *C. elegans* Chemosensory Neurons

We are interested in understanding how the functions of chemosensory neurons are specified during development. What molecular instructions determine neuron identity? How do sister-neurons adopt different fates? To address these questions, we have identified and characterized *C. elegans* mutants defective in sensory neuron development. Our approach was to mark particular chemosensory neurons *in vivo* using green fluorescent protein (GFP) expressed under the control of chemosensory neuron-specific promoters. We have carried out screens using promoters specific for either the AWA neurons, which sense a subset of volatile attractants, or the polymodal ASH neurons. Strains of worms with these GFP constructs were mutagenized, and mutants showing aberrant marker expression were isolated.

From these screens, we isolated four phenotypic classes of mutants: mutants in which expression of the *marker::GFP* construct was faint or absent, mutants with ectopic expression, mutants with cell position defects, and mutants with axon or dendrite defects. Ten mutants have been isolated which show faint marker expression in AWA or ASH, and many also show defects in neuronal function. Some of these mutants identified known transcriptional regulators.

We also isolated mutants with ectopic neuronal expression of AWA markers. One of these mutants, *sns-3(oy10)* (defects in sensory neurons specification), was the focus of my talk. We have isolated three mutants, *snd-1*, *snd2*, and *snd3* (sensory neuron defective) with abnormal chemosensory cell positioning. In addition, we have isolated four mutants with abnormal axons and/or dendrites.

We hope that by identifying and characterizing the mutants from this screen, we will gain an understanding of how the functions of the chemosensory neurons are specified during development.

Developmental Divergence of the Enteric and Sympathetic Nervous Systems

In the peripheral nervous system, enteric and sympathetic neurons develop from multipotent crest cells. While local environmental signals in the gut and in the region of the sympathetic ganglia play a role in the choice of cell fate, little is known about the mechanisms that underlie restriction to specific neuronal phenotypes. We investigated the divergence and restriction of the enteric and sympathetic neuronal lineages using immuno-isolated neural crest-derived cells from the gut and sympathetic ganglia. Analysis of neuronal and lineage-specific mRNAs and proteins indicated that neural-crest-derived cells from the gut and sympathetic ganglia had initiated neuronal differentiation and phenotype divergence by E14.5. We investigated the developmental potential of these cells using expression of tyrosine hydroxylase as a marker for sympathetic phenotype. Tyrosine hydroxylase expression was examined in neurons that developed from sympathetic and enteric neuroblasts under the following culture conditions: culture alone; co-culture with gut monolayers to promote oradrenergic differentiation; or co-culture with dorsal aorta monolayers to promote noradrenergic differentiation. Both enteric and sympathetic neuroblasts displayed developmental plasticity at E14.5. Sympathetic neuroblast down-regulated tyrosine hydroxylase in response to signals from the gut environment and enteric neuroblasts increases expression of tyrosine hydroxylase when grown on dorsal aorta or in the absence of other cell types. Tracking of individual sympathetic cells displaying a neuronal morphology at the time of plating indicated that neuroblasts

retained phenotypic plasticity even after initial neuronal differentiation had occurred. By E19.5 both enteric and sympathetic neuroblasts had undergone a significant loss of their developmental potential, with most neuroblasts retaining their lineage-specific phenotype in all environments tested. Together our data indicate that the developmental potential of enteric and sympathetic neuroblasts becomes restricted over time and that this restriction takes place not as a consequence of initial neuronal differentiation but during the period of neuronal maturation. Further we have characterized a default pathway of adrenergic differentiation in the enteric nervous system and have defined a transient requirement for gut-derived factors in the maintenance of the enteric neuronal phenotype.

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Clock Cells in the Fruit Fly *Drosophila* Revealed by Clock- Gene Expression

Circadian rhythms are the daily cycles of biomedical, physiological, and behavioral activities exhibited by many species from microorganisms to humans. The fundamental properties of this system are the following: the rhythms persist in constant environmental conditions such as constant light and constant temperature; the period of a rhythmic activity in a constant condition is approximately 24 hours, and this period is constant over a relatively wide range of temperature, and phases of these rhythms can be reset by an environmental stimulus such as a brief light pulse. These properties of the circadian systems are remarkably similar in organisms as diverse as plants and mammals. However, some organisms are suitable for studies at the level of tissue, and others are more suitable at the level of cellular and molecular studies. For instance in vertebrates, anatomical locations of the circadian pacemaker tissues have been studied intensively by surgical studies. While these surgical studies were successful in defining pacemaker structures, identification of the pacemaker cells within a structure was difficult.

In *Drosophila*, studies of circadian rhythms have been mainly at the molecular level rather than at the cellular or tissue level. Several genes that are involved in the pacemaking mechanism of the circadian clock have been identified. Recently, homologues of these molecular mechanisms of the circadian clock genes have been isolated in humans and mouse, suggesting a similarity in the molecular mechanisms of the circadian clock in insects and in mammals. Among these genes, the

period (per) and *timeless (tim)* genes have been studied intensively in flies. This made it possible to define the locations of putative pacemaker cells in this organism by monitoring spatial and temporal expression patterns of RNA and protein products of these genes. Numerous cells were found to express *per* and *tim* cyclically throughout the body of the fly. While many of these cells are putative pacemaker cells of unknown physiological function, some of the neurons in the brain are involved in the rhythmicity of fly's locomotor activity.

The first part of my work was focused on the expression patterns of *per* and *tim* proteins in brains of developing fruit flies. In the putative pacemaker brain neurons, these proteins oscillate in their amount. Surprisingly, the oscillations of these proteins in different cells were out-of phase. This result implies the presence of multiple oscillators involved in rhythms of different physiological or behavioral processes in a single organism. The second part of my work is anatomical characterization of the wiring patterns of the pacemaker neurons. This study gives an insight into the pathways from the pacemaker neurons to various tissues that are involved in circadian outputs.

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Human Theta Oscillations Show Task Dependence during Virtual Maze Navigation

Theta (4-8 Hz) oscillations have long been observed in animals during spatial navigation and are thought to be intimately involved in such tasks. However, strong evidence of task-dependent theta in humans has not been found. In an attempt to evoke task-dependent theta in humans and to characterize its functional role, we devised a spatial navigation task, for use with humans, that resembles tasks that elicit strong theta in rodents. We recorded from arrays of intracranial electroencephalographic (iEEG) electrodes during a virtual spatial navigation task. iEEG offers direct access to ventral brain regions as well as improved spatial resolution and less signal distortion and artifact than scalp EEG.

We tested three patients suffering from medically intractable epilepsy. Arrays of intracranial electrodes were implanted subdurally to localize the epileptogenic focus and identify functional regions to be avoided in surgery. The placement of the electrodes was determined by the clinical team. We sampled a total of 171 electrodes across the patients bilaterally in orbitofrontal and temporal cortex plus scattered locations in occipital and parietal cortex.

Subjects learned to navigate through visually rich, computer-rendered mazes. Each maze comprised a series of corridors, each leading to a T-junction. The subject's aim was to use arrow keys to navigate as quickly and accurately as possible from a starting point to a goal position. Subjects traversed each maze in study mode, in which arrows placed on the walls showed the correct path, and in test mode, in which the arrows were removed.

A dramatic feature of the raw iEEG trace, apparent upon visual inspection, is the appearance of episodes of rhythmic slow-wave activity interrupting the complex waveform. These oscillations are in the theta range (4-8 Hz) and appear during study and test trials in all three patients, and in many brain regions.

A prominent characteristic of these oscillations is that rather than being modulated continuously, they arise in distinct, well-defined episodes. We compared how many theta episodes occurred during longer, more difficult mazes and shorter, easier mazes. For each of our subjects, at certain cortical loci, percentage time in theta episodes was significantly greater during long mazes than short mazes, but no electrodes showed the reverse relationship. Additionally, many brain regions showed significantly more percentage time in theta episodes during test than study trials.

Recording from subdural electrodes, we observed significant increases in theta activity during virtual maze navigation. The theta activity appears in distinct episodes that become more frequent as the task becomes more difficult, suggesting that theta oscillations play a functional role in tasks similar to the spatial navigation tasks that evoke theta oscillations in rodents.