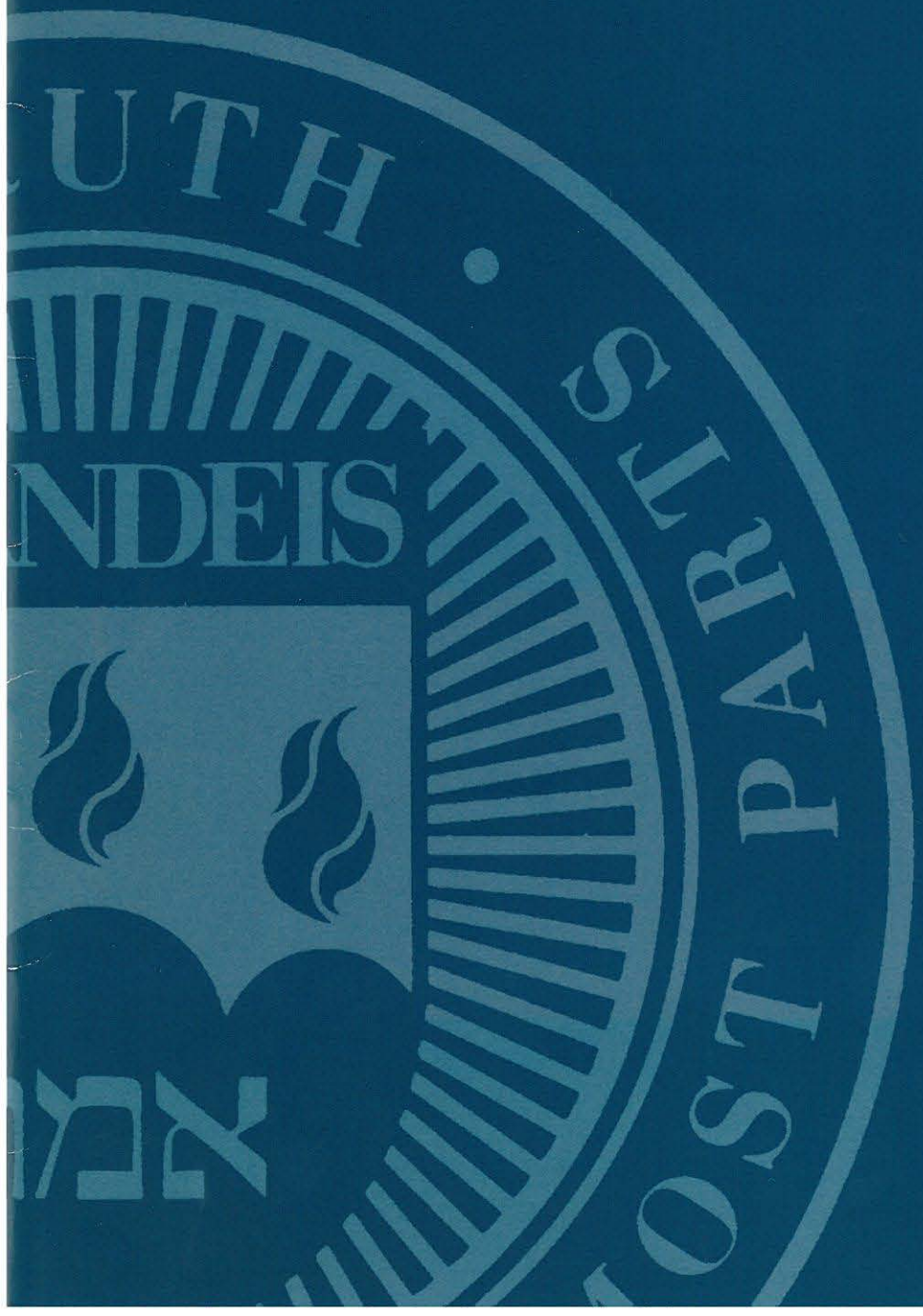
Brandeis University

The Volen National Center for Complex Systems

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

August 2001



The 2001 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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Introduction

The 2001 M.R. Bauer Foundation Colloquium Series, Scientific Retreat, and Distinguished Guest Lecturer Series

One of the most important parts of the Volen National Center's mission is to disseminate the results of its rapidly evolving work and to provide a forum to discuss them. It is a pleasure, therefore, to present this year's proceedings of the M.R. Bauer Foundation Colloquium Series, Scientific Retreat, and Distinguished Guest Lecturer Series at Brandeis University's Volen National Center for Complex Systems. Now in its seventh year, the generous support of the M.R. Bauer Foundation has made possible an impressive series of lectures and informal interactions that have served to reflect some of the most compelling new developments in neuroscience. My colleagues and I would like to express our appreciation to the M.R. Bauer Foundation for its continuing support that has enabled the faculty and students of the Volen Center to share their work with, and learn directly from, many of the leading practitioners in the field.

The range of topics addressed in the 2000-01 M.R. Bauer Colloquium Series was impressive. Dr. Paul Worley, from the Department of Neuroscience and Neurology at the Johns Hopkins University School of Medicine, discussed his work on molecular mechanisms activated by nerve cell response to specific environments. Using a new assay method that can identify sub-groups of neurons within the same region of the brain, he provides a novel glimpse into how the external environment is represented by a network of brain cells. Dr. Simon Giszter of Hahnemann University's Department of Neurobiology and Anatomy explored the concept of force-field primitives as a new framework for understanding the psychophysical basis of human movement. Force fields generated by biological systems may be seen as the "building blocks" of movement, a way the organism chooses from among the multitude of possible options in executing motion. Dr. Kathleen Dunlap, from the Department of Physiology at Tufts University School of Medicine, talked about the important role of a class of proteins in inhibiting calcium ion channels and thereby activating the release of transmitter chemicals essential to certain neural processes. She showed that G-proteins bind directly to calcium channels, a process that induces a transient inhibition of channel activity in neurons. Dr. Ueli Schibler from the University of Geneva's Department of Molecular Biology explained how peripheral organs appear to have their own biological clocks that are reset daily by exposure to daylight. The liver's molecular clock, for example, drives the production of enzymes at particular times in anticipation of food consumption. Dr. Schibler noted that much of the work explaining the mechanisms that produce the molecular oscillations generating circadian rhythms has been done at Brandeis.

Dr. Anthony Wagner from MIT's Department of Brain and Cognitive Sciences delivered a talk about why we remember certain experiences and not others. Looking specifically at the recall of verbal experiences, he identified processes in the left prefrontal cortex that play a critical role in memory regardless of variables such as attention. Dr. Dan Johnston from the Baylor College of Medicine's Division of Neuroscience described how scientists are beginning to recognize the ways that dendrites, the long branches of neurons that receive impulses, determine the mechanisms of synaptic plasticity by which the brain learns and adapts to experiences. He emphasized how completely the brain cell can control its own synaptic strength and therefore help to remember past events and incorporate new ones as experiences warrant. Dr. Ranulfo Romo from the University of Mexico's Department of Neuroscience described efforts to understand the cellular basis of perception and cognition. His goal is to unravel the patterns of neuronal firing in the cortex that may reveal how monkeys make simple decisions. Taken together, the talks in the M.R. Bauer Colloquium Series served to highlight some of the emerging developments of neuroscience.

Now in its third year, the M.R. Bauer Distinguished Guest Lecturer Series brought to campus two of the most eminent scientists in the field. Professor Roger Nicoll, a member of the National Academy of Sciences, is the Morris Herzstein Professor at the University of California, San Francisco, and a member of UCSF's W.M. Keck Foundation Institute for Integrative Neuroscience. He is well known for having shown how drugs and transmitter chemicals work in the nervous system, for revealing the subtlety and complexity of signaling in the brain, and for providing new insights into the plasticity of the central nervous system. Nicoll's visit coincided with the Volen Center's annual M.R. Bauer Foundation Scientific Retreat at Woods Hole, Massachusetts, at which he presented the keynote lecture. Nicoll's talk, on "Presynaptic Plasticity and the Redistribution of Glutamate Receptors," showed how important certain receptors are to the processes of learning and memory. In a separate talk, he also shed light on the role that drugs such as marijuana play in changes in cognitive function.

This year's second M.R. Bauer Distinguished Guest Lecturer was William T. Newsome III, professor of neurobiology at the Stanford University School of Medicine. An Investigator of the Howard Hughes Medical Institute and a member of the National Academy of Sciences, Newsome has provided a deeper understanding of the way in which neural mechanisms mediate basic cognitive functions such as motion perception. He is widely renowned for work that relates cellular function in the primate brain to behavior. His public lecture, "From Neurons to Perception," presented convincing evidence, based on his long-term research on the visual system, that linked the firing of individual neurons to behavioral judgments with respect to directional movement. He also demonstrated that vision is created when the brain chooses the neuron that is working most effectively, rather than averaging all the signals of visual neurons. Newsome's findings may prove important for the development of treatments for blindness and neurological disorders.

The 2001 Volen Center Retreat sponsored by the M.R. Bauer Foundation focused on "consciousness." Held at the Marine Biological Laboratory at Woods Hole on February 20 and 21, the retreat featured a lecture by the Bauer Distinguished Guest Lecturer Professor Roger Nicoll (described above), as well as a special presentation by Dr. Hod Lipson of Brandeis's computer science department. Lipson, who works with Professor Jordan B. Pollack of Brandeis's computer science department, talked about their breakthrough in creating robots that can autonomously design and fabricate new robots, which received front-page coverage in *The New York Times* in August 2000. In his talk at the retreat, "Automatic Design and Manufacture of Robotic Lifeforms," he elaborated the experiments through which they created systems that can sustain their own evolution. Their work represents the first time that an artificial evolution system has been connected to an automatic physical construction system. They created an evolutionary computational process by which fitter machines were selected from a population of 200 candidate robots. While many further steps would be needed before this technology might become dangerous, it is clear that these robots cross the simulation-reality gap and affect the physical world directly. Future work will be focused on understanding how more complex structures might self-organize and how these machines may be made under the control of the evolutionary process.

A panel discussion, involving Professor of Biology John Lisman, Associate Professor of Philosophy Jerry Samet, and neuroscience graduate student Chaelon Myme, addressed a central question of consciousness: How does the brain represent the world in our minds? Samet provided an overview of the history of the study of consciousness by philosophers from Descartes to the present. Lisman spoke about the underlying mechanisms of consciousness, particularly a neural receptor that is essential to working memory, perhaps the most important element in consciousness. He is optimistic about the possibility of applying rigorous scientific approaches to the study of consciousness. Myme described the "neural correlates of consciousness," and suggested that the circuitry of the inferotemporal (IT) cortex in the brain may be found to provide the neural mechanisms of consciousness. While some participants at the retreat thought it might be premature to describe consciousness in mechanistic terms, links between widely separated disciplines are beginning to be established. The 2001 M.R. Bauer Scientific Retreat helped faculty and students to think about the larger issues that frame their research, and underscored why the Volen Center's interdisciplinary approach has proven to be so successful.

Having completed seven years, the M.R. Bauer Foundation Colloquium and Scientific Retreat have been highly effective in promoting the exchange of ideas and methods across disciplinary boundaries, in advancing the study of neuroscience, and in fostering a sense of community among the neuroscientists at Brandeis and elsewhere. The M.R. Bauer Distinguished Guest Lecturer Series has added a new dimension to these activities over the past three years. These published proceedings represent a major element in the Volen Center's effort to encourage scientific collaboration and discussion. I am especially pleased to thank the M.R. Bauer Foundation for supporting these important activities.

Leslie Griffith, M.D., Ph.D.
Associate Professor of Biology and Acting Director, Volen National Center for Complex Systems

Paul Worley, M.D.
Department of Neuroscience and Neurology
Johns Hopkins School of Medicine
Baltimore, Maryland
September 11, 2000

IEGs and Excitement at the Synapse

Paul Worley and his lab have made, and continue to make, significant contributions to neuroscience. In particular, his contributions have furthered our understanding of the molecular mechanisms activated in response to nerve cell activity.

Worley's lecture centered around a screen looking for genes that were up-regulated in response to neuronal activity. This screen resulted in the discovery of an activity dependent IEG Arc (activity-regulated cytoskeletal associated protein).

Since its initial discovery, the Worley lab's efforts studying Arc have been fruitful. Using a new technique called catFISH they were able to view a history of activity in CA1 neurons that had been activated in response to exposing an animal to specific environments and probing with an Arc antisense probe.

Animals were exposed to a one environment initiated Arc mRNA expression in a sub-set of the total neurons in the CA1. Re-exposing animals to the same environment activated the very same sub-population of neurons. However, when animals exposed to one environment were then introduced to a novel environment, the introduction resulted in an equivalent size of activated Arc mRNA, but occurred in a different population of neurons. This provides a glimpse into how the external environment is represented by a network of activated neurons within the brain. The catFISH assay is a breakthrough because this resolution of sub-populations of neurons within the same region of the brain would not be possible using the conventional imaging techniques such as fMRI and PET.

Worley discussed some of the technical limitations of the assay, mentioning that because the Arc mRNA is degraded within a half hour, he and his colleagues were restricted to a very small window of time in which to perform the assay. However, efforts are underway to use the Arc promoter—which is activated very quickly in response to neuronal activity—to control other genes that have a longer half-life. This, in turn, will allow Worley and his lab to examine a longer history of the activated neurons.

Simon Giszter, Ph.D.
Department of Neurobiology
and Anatomy
Hahnemann University
Philadelphia, Pennsylvania
October 2, 2000

Movement Control by Summation of Force-Field Primitives

Movement control is faced with a number of computational problems that arise from kinematic and kinetic redundancy—the multitude of ways in which a given motion can be executed. Spinal microstimulation studies indicate that the frog spinal cord might be organized into modules that produce force-field primitives.

Based on these initial findings, Bizzi, Giszter, and Mussa-Ivadi proposed that diverse and redundant movements arise from combinations of these primitives. Giszter went on to describe studies in which he and colleagues examined how the frog uses the force-field primitives to construct the correction response during wiping reflex. They recorded the force field generated by the frog during wiping reflex with cutaneous feedback intact and after cutaneous deafferentation. By subtracting force field under these two conditions, they got the corrective force field.

There are two lines of evidence that the frog generates the corrective response by summing the corrective force field with the normal wiping reflex force field: first, the correlation of the force field across different time points is high; second, the rise and fall of force magnitude at each location is unimodal. In addition to this, they also identified the muscle synergy responsible for the corrective response. In conclusion, force-field primitives may be used as building blocks by biological systems to deal with the kinematic and kinetic redundancy in movement control.

It is important to note, however, that the situation may not be as simple when it comes to higher vertebrates, especially humans. For example, the influence of gravity may differ when the arm is in different configurations. Therefore, the formation of a trajectory cannot be explained solely by the force field. Nevertheless, the concept of force-field primitives may provide a new framework in which to understand psychophysical studies of human movement.

Kathleen Dunlap, Ph.D.
Department of Physiology
Tufts University School of Medicine
Boston Massachusetts
October 10, 2000

Calcium Channels

Voltage-gated Ca2+ channel activity is modulated by a variety of substances in many different pathways. Dunlap's research focuses on G-protein-coupled pathways involved in modulation of N-type Ca2+ channels. Some of these pathways involve direct binding of G-protein subunits to calcium channels, which induces a transient voltage-dependent inhibition of N-type channel activity.

Other pathways involve intermediate enzymes and induce long-lasting voltage-independent inhibition of N-type channels. It is known that G-protein subunits act as mediators of receptor-effector coupling and that G-$\alpha\beta\gamma$ are involved in regulation of effectors. The number of different genes encoding G-$\beta\gamma$ had suggested a possible selectivity of these different G-$\beta\gamma$ subunit types for different effectors, but no previous studies clearly support any selectivity. Dunlap's group has recently found evidence for such selectivity in vivo, by using recombinant G-$\beta\gamma$ complexes in chick sensory neurons.

Specifically, G-$\beta\gamma$ complexes containing one β subunit activate the phospholipase Cβ pathway (PLCβ) inducing N-type Ca2+ current inhibition, whereas G-$\beta\gamma$ complexes containing a different β subunit have no effect. Interestingly, this selectivity is not observed with an in vitro enzyme assay, suggesting that intact cell may contain modulating factors that selectively enhance interactions between effectors and particular G-$\beta\gamma$ complexes.

Overall these experiments show that selective activation of pathways inhibiting N-type Ca2+ channels by G-$\beta\gamma$ complexes may play an important role in neural processes such as transmitter release.

Ueli Schibler, Ph.D.
Department de Biologie Moleculaire
Sciences II
University of Geneva
Geneva, Switzerland
December 11, 2000

Circadian Rhythms: How Does the Liver Tell Time?

Circadian rhythms are cyclical changes in physiology, gene expression, and behavior that run on a cycle of approximately one day (even in conditions of constant light or darkness). Schibler's talk focused on the observation that many peripheral organs in the body appear to have their own molecular clocks that are reset daily by exposure to daylight. A central clock which, in mammals, is located in the Suprachiasmatic Nucleus (or SCN, a region of the hypothalamus) coordinates the resetting of the peripheral clocks.

Some examples of output from these clocks are the daily rhythmic changes in body temperature, blood pressure, heart rate, concentrations of melatonin and glucocorticoids, urine production, acid secretion in the gastrointestinal tract, and changes in liver metabolism. In the case of the liver, its molecular clock drives the production of enzymes at specific times during the day (or night, in the case of rats) in anticipation of food consumption.

Schibler pointed out that much of the work done elucidating the mechanisms that produce the molecular oscillations generating circadian rhythms has been done here at Brandeis in the labs of Michael Rosbash and Jeffrey Hall. Specific transcriptional regulators, genes discovered first in *Drosophila* with their homologs later identified in mammals, are shown to drive these molecular oscillations based on negative feedback loops of gene expression. Measuring levels of transcribed mRNA for these clock genes at different times during the day is another way to quantify the timing of a clock at the cellular level.

Individual cells in culture can be induced to produce rhythmic gene expression, and these rhythms persist running on their own for days. The central (SCN) and peripheral (liver) clocks have different entrainment properties, which means their rhythms can be differentially effected by changes in environment. For example, if you shift the feeding time for a mouse from night to day, it will shift the peripheral clock in its liver over a period of days to anticipate the new feeding time, thus completely inverting the original phase relationship. However, the central clock will not shift in its rhythmic transcription of circadian genes.

Recent findings from the Schibler lab suggest a role for glucocorticoids as a signal from the SCN to the liver. The absence of glucocorticoid signaling results in a much faster phase-shifting in response to daytime feeding in mice. Therefore, one role of this signal seems to be to slow the phase shifting in peripheral clocks in response to changes in feeding time.

Thus, if you decide to have a large, late night snack, it would not be sufficient to shift the circadian clock in your liver, due in part to release of glucocorticoids from the SCN. Other potential signals from the SCN have yet to be uncovered and the mechanism by which the SCN resets peripheral clocks needs to be explored in further detail.

Anthony Wagner, Ph.D.
Department of Brain and
Cognitive Sciences
Massachusetts Institute of Technology
Cambridge, Massachusetts
January 22, 2001

Control of Memory: The Role of Prefrontal Cortex in Long-Term Memory

A fundamental question about human memory is why some experiences are remembered whereas others are forgotten. Episodic memory is often described as the conscious memory for personal everyday experiences. Episodic encoding, therefore, refers to the processes by which an experience is transformed into an enduring memory trace.

Psychological studies have shown that the memorability of an experience is influenced greatly by the cognitive operations engaged during initial encoding of that experience. For example, semantic processing leads to superior memorability relative to nonsemantic processing. Lesion studies have shown that damage in the prefrontal cortex results in modest episodic deficits, specifically in terms of executive control of cognitive functions. Typical studies of brain-injured amnesic patients, however, cannot clearly distinguish between the effects of brain damage on the encoding of memories and their retrieval from storage.

An additional line of evidence for the role of prefrontal cortex in episodic encoding, therefore, comes from functional neuroimaging studies. These studies have implicated left prefrontal cortex in verbal encoding. It has been shown that left prefrontal activation is greater during semantic encoding relative to nonsemantic encoding. Additionally, left prefrontal participation decreases and memorization is impaired when semantic encoding operations are disrupted.

Typically, these studies have relied on blocked experimental designs, where trials from each encoding condition are presented sequentially, inseparable from each other during the functional scan. While blocked designs allow comparison between encoding conditions that yield, on average, higher or lower levels of subsequent recollection, they do not allow a direct trial-by-trial comparison between specific encoding trials that lead to subsequent remembering and those that lead to subsequent forgetting.

Results from event-related potential (ERP) studies, which allow for trial-by-trial analysis, suggest that the neural signature during verbal encoding differs for subsequently remembered and subsequently forgotten experiences, with remembered experiences being associated with a greater positive-going response over frontal and parietal regions. However, ERP studies are characterized by limited spatial resolution. Thus, the precise functional neuroanatomic encoding differences that predict whether a particular verbal experience will be remembered or forgotten are currently unknown.

To address these issues, the neural correlates of incidental word encoding were examined in two whole-brain functional magnetic resonance imaging (fMRI) studies. One experiment used blocked-design procedures to investigate how systematic manipulation of the encoding task affects prefrontal activation, whereas the other used newly developed event-related procedures that allow direct comparison between specific encoding trials that result in subsequent remembering and forgetting.

Results revealed that what makes a verbal experience memorable partially depends on the extent to which left prefrontal regions are engaged during the experience. Verbal experiences may be more memorable when semantic and phonological attributes of the experience are extensively processed via participation of left prefrontal regions. These regions may serve to organize these attributes in working memory.

A specific experience may elicit the recruitment of these processes to a greater or lesser extent because of variable task demands, shifts in subjects' strategies, characteristics of target items, or attentional modulations. Regardless of the source of this variability, greater recruitment of left prefrontal processes will tend to produce more memorable verbal experiences.

Dan Johnston, Ph.D.
Division of Neuroscience
Baylor College of Medicine
Houston, Texas
January 29, 2001

Role of Active Dendrites in Synaptic Integration and Synaptic Plasticity

Synaptic plasticity has long been thought to be the mechanism by which the brain learns and adapts to experiences. The neurons of the brain must arrange themselves in specific connections called synapses that the brain must maintain over time, yet also allow for plasticity of these connections such that they can be strengthened or weakened as new experiences are integrated. Recently, the dendrites of the neurons have become increasingly recognized as determining the mechanisms of synaptic plasticity.

One particular area of interest is in back-propagating action potentials, voltage spikes that travel backwards up the dendrites towards the inputs from the other neurons. Johnston's group believes that the ion channels involved in back-propagating spikes might also be involved in the plasticity of the synapses. Johnston described one type of ion channel, the A-type potassium channel, which strongly controls back-propagation.

Johnston showed that during one of these back-propagating spikes, the A-type potassium channel opens briefly to let potassium ions out of the cell. This outward current is key to keeping the voltage spike that travels up the dendrite from getting very large.

Johnston also described how the brain's neuromodulators could change the A-current. Protein kinase A, protein kinase C and mitogen-activated protein kinase can all change the effectiveness of this ion channel. Johnston's group believes that by changing the efficiency of the ion channel, they can change the size of the back-propagating spike.

When a synapse is strengthened, such as is suspected in learning, it is said the synapse has become potentiated. If this strengthening is long-lasting, it is called long-term potentiation. When a back-propagating spike occurs at the same time that input arrives in the dendrites, there is often long-term potentiation. Johnston's group found that the same enzymes that manipulate the A-type potassium channel could indeed change the size of the spike. Moreover, when they apply inhibitors to these enzymes, they could prevent long-term potentiation from occurring. Therefore, it appears that these potassium channels play an important role in synaptic plasticity.

By having a varied density of these A-type potassium channels along the dendrites, the neuron can control the size of the back-propagating spike, and thus control how much plasticity there is at a synapse. The results described by Johnston during his lecture emphasized how completely the cell is able to control its own synaptic strength; by regulating its ion-channel density, by adjusting any of several enzyme pathways, or even by responding to the specific timing of inputs to the synapse. In doing so, the brain can remember past events and incorporate new ones as experiences warrant.

Ranulfo Romo
Professor, Instituto de Fisiología Celular
Universidad Nacional Autónoma de México
México City, México
May 7, 2001

Probing the Cortical Evidence of a Sensory Discrimination Task

An important goal of neuroscience research is to understand the cellular basis of perception and cognition.

To this end, Romo has monkeys carry out a sensory discrimination task, in which they must make a motor response dependent on their comparison of two somatosensory stimuli. The stimuli consist of 10-40Hz vibrations on the monkey's forefinger, which lead to a perception of "flutter." The monkey experiences a "cue" stimulus, then after a delay of one to six seconds must discriminate whether a second, "response" stimulus has a higher or lower frequency. The monkey receives a juice reward if it makes the correct motor response by pulling one of two levers corresponding to higher or lower response frequency.

This task is valuable, as it requires the monkey to carry out the most basic of perceptual and cognitive tasks—that is, to compare two quantities. It was important that the cue and the response frequencies were varient at random. Without variation of the cue stimulus, the monkey would avoid true comparison, and more simply categorize the response frequency as "high" or "low" based on a previously learned rule.

During the trials, extracellular recordings of neurons in somatosensory, prefrontal, and primary motor cortices demonstrated that neuronal activity correlates with the task. Romo's group has shown that during the stimulus, the period of neuronal rhythmic activity in the primary somatosensory cortex (S1) contains more information about stimulus frequency than does the average firing rate (which increases monotonically with stimulus frequency).

However, the monkey's psychophysical performance in the task matches the information based on an average rate code. Further evidence that the monkey's perception of frequency is based on the average firing rate of neurons in S1 was provided by showing that neurons in the secondary somatosensory cortex (S2) do not fire with the periodicity of the stimulus. Moreover, the monkey was able to perform the task equally well with an aperiodic stimulus, when there can be no rhythmic activity of neurons, by comparing the average frequencies.

A groundbreaking success in these experiments was achieved by using electrical stimuli of rapidly adapting neurons in S1 to mimic the vibrotactile stimulus. When electrical stimuli were used in the place of the mechanical vibrations, for either the cue or the response in the trial, Romo's group observed no deterioration in performance. Hence, they were able to bypass the monkey's sensory system and inject the information directly into its cortex!

Interestingly, they found neurons in S2 and the prefrontal cortex, whose firing rates decreased with increasing stimulus frequency, such that they encoded the stimulus in a negative monotonic manner. Many neurons in the prefrontal cortex (PFC), an area known to exhibit the persistent activity necessary for working memory, maintained task-related activity throughout the delay period of up to six seconds. Other PFC neurons, along with neurons in S2, fired at a stimulus-dependent rate only during the cue, and at the beginning of the delay, decaying to spontaneous rates after about one second. Yet other PFC neurons, as well as neurons in the primary motor cortex ramped up their activity during the final second of the delay, and fired at higher rates during the "response" stimulus. The goal is to unravel the patterns of neuronal spiking, to distinguish the activities that encode the perception and memory of a cue stimulus, the comparison of cue and response stimuli, and the preparation of motor action. They hope to understand how a monkey makes the simplest of decisions.

The M.R. Bauer Distinguished Lecturer Series Summaries 2001

Introduction

One of the highlights again this year has been the M.R. Bauer Distinguished Guest Lecturer Series. This program, now in its third year, brought to campus two outstanding people, both well-known neuroscientists—Roger Nicoll, professor of physiology and cellular and molecular pharmacology at the University of California in San Francisco, and Bill Newsome, a professor in the Department of Neurobiology at the Stanford University School of Medicine.

Both guests spent a full week at Brandeis. Their schedules were full with a public lecture, presentations at journal clubs, meetings with class sessions, graduate students and postdoctoral fellows, and spending time in many neuroscience laboratories. Feedback from our students clearly indicates what a privilege it is to have these world-class scientists spending this amount of time on campus, getting to know the students, and providing invaluable advice to these younger scientists. Both weeks were very busy, informative, and enjoyable for all.

Roger Nicoll, M.D.

Department of Cellular and
Molecular Pharmacology
University of California, San Francisco
San Francisco, California

February 19-23, 2001

Presynaptic Neurotransmitter Receptors and the Control of Transmitter Release

For the week of February 19-23, Dr. Roger Nicoll from UCSF was a visiting professor at Brandeis. On Monday, February 19, Nicoll presented his research in a Bauer Lecture. His topic, "Presynaptic Neurotransmitter Receptors and the Control of Transmitter Release," focused on two different types of plasma membrane receptors, which act to modulate synaptic transmission between hippocampal neurons.

The first half of the talk described a long-lasting, facilitatory role for kainate receptors on Granule cell synapses (also called Mossy fiber synapses) in area CA3 of the hippocampus. These receptors act presynaptically as autoreceptors at these synapses to facilitate further release of the excitatory neurotransmitter glutamate. This mechanism is relatively novel because kainate receptors are ionotropic receptors, which can mediate fast effects on ionic conductance. Prior research on presynaptic receptors in the brain have shown their effects to be mediated mainly through metabotropic receptors, which activate G-proteins and other molecular mechanisms in the cell, resulting in a slower and more long-lasting cellular response. The activation of presynaptic kainate receptors appears to be part of a positive feedback loop. High levels of glutamate released by the granule cell activate kainate receptors on its own presynaptic terminal. The activated kainate receptors further increase the release of glutamate.

For the second half of the lecture, Nicoll focused on describing the physiological function of cannabinoid receptors in the brain. Cannabinoid receptors were originally discovered to be the receptor that Cannabis sativa, or marijuana, binds to in the brain. It can be found on a subset of inhibitory interneurons (which release GABA) in the hippocampus called basket cells, located in the pyramidal cell layer.

Since their discovery, endogenous ligands for this receptor have been discovered and their effect on cellular function has been examined. The activation of these receptors on these GABAergic neurons results in a calcium-dependent, depolarization-induced suppression of inhibition (DSI), which decreases the frequency of spontaneous miniature IPSPs, thus decreasing the probability of GABA release from these interneurons. These basket cells make synaptic contacts onto neighboring pyramidal cells in the hippocampus and are involved in the entrainment of pyramidal cells and in the modulation of theta-wave activity in the hippocampus. Nicoll's findings can potentially shed some light on the role that Cannabinoids play in changes in cognitive function.

William T. Newsome III, Ph.D.

Department of Neurobiology
Stanford University School of Medicine
Stanford, California

April 23-28, 2001

From Neurons to Perception

To investigate the neural basis of visual behavior one needs to compare neurophysiological events in the visual cortex with the visual psychophysical performance of an animal. It may be possible to determine which neural structures are responsible for a particular aspect of perception if one can readily demonstrate a correlation between a neuron's activity and an animal's responses.

Dr. William Newsome has done this in the most direct way—he performed concurrent psychophysical and electrophysiological experiments in awake behaving macaque monkeys. Measuring single cell properties in some cortical structures can provide insight into the perceptual function of that structure.

Newsome studied the properties of neural cells in the medial-temporal (MT) cortical area of the macaque visual cortex while the animal performed a psychophysical task. The MT area is organized into columns of cells selective for the direction of movement of a visual target.

To stimulate these cells, a random-dot moving display was used in which the fraction of coherently moving dots could be systematically varied. At 0% coherence all dots moved randomly, while at 100% coherence all dots moved with uniform speed in the same direction. Thus at 50% coherence half of the dots in the display moved at the same velocity while the other half moved randomly.

After a cluster of cells in an MT column were found and their preferred direction and receptive field determined, the cells' percentage of coherence threshold was determined by electrophysiologically recording the responses to moving-dot displays of different coherence levels. Concurrently, the monkey performed a two-alternative forced choice psychophysical task whereby he responded to the perceived movement of the dots in the receptive field of the recorded cells by making saccades in the appropriate preferred or null direction. The monkey's psychophysical threshold and psychophysical curve corresponded well with that of the recorded cluster of MT neurons, implying strongly that the performance of these MT neurons underlies the psychological performance of the animal.

In order to further test the idea that these neurons' activity provides the neural basis for the animal's motion perception, Newsome went on to study how altering the cells' activity affected the performance of the whole animal. Running the same psychophysical task, an identified cluster of directional cells in an MT column was electrically stimulated while the animal viewed the moving-dot stimulus. It was found that the animal's two-choice responses were biased towards the preferred direction of the stimulated cortical neurons.

This result undoubtedly demonstrated that the activity of a small number of cells does determine the animal's performance. However, it is harder to tell from this work whether the stimulation of these neurons caused an alteration in the perception of motion of the display or in the process of decision making independent of what direction was perceived.

Besides direction selectivity, many cells in area MT also code for retinal disparity, a measure of the location of an object in depth. Using similar psychophysical paradigms adapted to test for performance on retinal disparity instead of direction of movement, Newsome and his colleagues found as before that the neural responses were at least as good as the performance of the monkey, and that stimulating a particular disparity column biased the animal's psychophysical performance accordingly. These results demonstrate that the neural basis of other aspects of visual perception is similar to motion direction perception. Thus, we may generalize this understanding to other related neuro-perceptual questions.

The 2001 Volen National Center for Complex Systems Scientific Retreat

"Consciousness"

Marine Biological Laboratory
Woods Hole, Massachusetts
February 20-21, 2001

Tuesday, February 20, 2001

2:00 pm
Arrival and check-in

4:30 pm
Poster session and refreshments
(second floor of Swope)

6:00 pm
Dinner

7:15 pm
Keynote Speaker
Roger Nicoll, M.D.
Professor of Physiology and Cellular and Molecular Pharmacology
University of California
San Francisco
"Synaptic Plasticity and the Redistribution of Glutamate Receptors"

8:30 pm
Music and dancing
(Meigs Room in Swope)

Wednesday, February 21, 2001

7:00 am
Breakfast

8:45-9:30 am
Hod Lipson, Ph.D.
Department of Computer Science
Volen National Center for Complex Systems
Brandeis University
"Automatic Design and Manufacture of Artificial Lifeforms"

9:30-10:00 am
Jerry Samet, Ph.D.
Associate Professor of Philosophy
Brandeis University
"Consciousness"

10:00-10:30 am
Break

10:30 am-12:00 pm
Panel Discussion on "Consciousness" with John Lisman, Chaelon Myme, and Jerry Samet

12:00 pm
Lunch

1:00 pm
Departure

Hod Lipson, Ph.D.
Department of Computer Science,
Volen National Center for Complex Systems
Brandeis University
Waltham, Massachusetts
February 21, 2001

Automatic Design and Manufacture of Robotic Lifeforms

Complex biological forms reproduce by taking advantage of an arbitrarily complex set of auto-catalyzing chemical reactions. Biological life is in control of its own means of reproduction, and this autonomy of design and manufacture is a key element that has not yet been understood or reproduced artificially. To this date, robots—forms of artificial life—are still designed laboriously and constructed by teams of human engineers at great cost. Few robots are available because these costs must be absorbed through mass production that is justified only for toys, weapons, and industrial systems like automatic teller machines.

In this discussion we report a set of experiments in which simple electro-mechanical systems evolve from scratch to yield physical locomoting machines. Like biological lifeforms whose structure and function exploits the behaviors afforded by their own chemical and mechanical medium, our evolved creatures take advantage of the nature of their own medium—thermoplastic, motors, and artificial neurons. We thus achieve autonomy of design and construction using evolution in a limited universe physical simulation, coupled to off-the-shelf rapid manufacturing technology. This is the first time robots have been robotically designed and robotically fabricated.

Our key claim is that to realize artificial life, full autonomy must be attained not only at the level of power and behavior (the goal of robotics, today), but also at the levels of design and fabrication. Only then can we expect synthetic creatures to bootstrap and sustain their own evolution. We thus seek automatically designed and constructed physical artifacts that are (a) functional in the real world, (b) diverse in architecture (possibly each slightly different), and (c) producible in short turn-around time, low cost, and large quantities. So far these requirements have not been met.

The experiments described here use evolutionary computation for design, and additive fabrication for reproduction. The evolutionary process operates on a population of candidate robots, each composed of some repertoire of building blocks. The evolutionary process iteratively selects fitter machines, creates offspring by adding, modifying, and removing building blocks using a set of operators, and replaces them into the population.

Our approach is based on use of only elementary building blocks and operators in the design and fabrication process. As building blocks are more elementary, any inductive bias associated with them is minimized, and at the same time architectural flexibility is maximized. Similarly, use of elementary building blocks in the fabrication process allows it to be more systematic and versatile. Starting with a population of 200 machines that were comprised initially of zero bars and zero neurons, we conducted evolution in simulation. The fitness of a machine was determined by its locomotion ability: the net distance its center of mass moved on an infinite plane in a fixed duration. The process iteratively selected fitter machines, created offspring by adding, modifying, and removing building blocks, and replaced them into the population. This process typically continued for 300 to 600 generations. Both body (morphology) and brain (control) were thus co-evolved simultaneously.

The simulator we used for evaluating fitness supported quasi-static motion in which each frame is statically stable. This kind of motion is simpler to transfer reliably into reality, yet is rich enough to support low-momentum locomotion. Typically, several tens of generations passed before the first movement occurred. Various patterns of evolutionary dynamics emerged, some of which are reminiscent of natural phylogenic trees.

Selected robots out of those with winning performance were then automatically replicated into reality: their bodies, which existed only as points and lines, were first converted into a solid model with ball-joints and accommodations for linear motors according to the evolved design.

This solidifying stage was performed by an automatic program that combined pre-designed components describing a generic bar, ball joint, and actuator. The virtual solid bodies were then materialized using commercial rapid prototyping technology.

In spite of the relatively simple task and environment (locomotion over an infinite horizontal plane), surprisingly different and elaborate solutions were evolved. Machines typically contained around 20 building blocks, sometimes with significant redundancy (perhaps to make mutation less likely to be catastrophic). Not less surprising was the fact that some exhibited symmetry, which was neither specified nor rewarded anywhere in the code; a possible explanation is that symmetric machines are more likely to move in a straight line, consequently covering a greater net distance and acquiring more fitness. Similarly, successful designs appear to be robust in the sense that changes to bar lengths would not significantly hamper their mobility.

In summary, while both the machines and task described in this work are fairly simple from the perspective of what human teams of engineers can produce, and what biological evolution has produced, we have demonstrated for the first time a robotic bootstrap, where automatically designed electromechanical systems have been manufactured robotically. We have carefully minimized human intervention both in the design and in the fabrication stages. Besides snapping in the motors, the only human work was in informing the simulation about the universe that could be manufactured.

This is the first time any artificial evolution system has been connected to an automatic physical construction system. Our evolutionary design system, solidification process, and rapid prototyping machine form a primitive "replicating" robot. While there are many, many further steps before this technology is dangerous, we believe that if indeed artificial systems are to ultimately interact and integrate with reality, they cannot remain virtual; it is crucial that they cross the simulation-reality gap to learn, evolve, and affect the physical world directly. Eventually, the evolutionary process must accept feedback from the live performance of its products.

Panel Discussion

February 21, 2001

"Consciousness"

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Jerry Samet, Ph.D.
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How does the brain represent the world in our minds? What does it mean to behave without awareness of our actions or ourselves? How can we experience the taste of strawberries, the moving crescendo of a symphony, the humor of a joke—all somehow through the workings of billions of nonconscious neurons? Long considered an indelicate topic for serious discussion in neuroscience circles, the past decade has yielded rapprochement between neuroscience and consciousness. Nobel laureates and dedicated consciousness conferences have championed this cause, coupled with a philosophy of mind resurgence and application of neuroscientific approaches to consciousness study. Our retreat hoped to get our complex systems community up to speed on what these key issues and approaches are.

Central to this mission was a 90-minute panel discussion on consciousness with Professors Jerry Samet (Department of Philosophy, Brandeis), John Lisman (Department of Biology, Brandeis), and neuroscience graduate student Chaelon Myme.

As a prelude to the panel discussion, Samet gave an overview of the history and key features of consciousness study in philosophy, from Descartes through a taxonomy of stances held today. His exposition nicely laid out the scope of the discussion so that the audience might engage the panelists in a more informed way.

Lisman began the panel with his ideas about a stringent and operationally defined approach to studying the mechanisms underlying consciousness. Espousing the importance of working memory to consciousness and the NMDA receptor to working memory, he argued that pharmacological disruption of NMDA function in human subjects via the NMDA blocker ketamine could yield insights about the mechanism of consciousness. He also spoke of unconscious processing during awake states, such as driving a car while deeply lost in thought, and overall spoke optimistically about the prospect of rigorous scientific study of consciousness.

Myme followed with an introduction to some of the recent neuroscience articles about what is being called "neural correlates of consciousness." He presented studies of binocular rivalry (where images "compete" for visual awareness) in monkey and in man, which suggest that the inferotemporal (IT) cortex is activated during those moments when an object is perceived, and not merely when it is activating the retina and initial stages of visual brain areas. Although admitting we were a long way off in getting to more than a coarse understanding of consciousnss, he suggested that if IT is a key brain area for visual awareness in humans and in monkeys, more thorough study of the microcircuitry of IT in primates may be useful for understanding not just neural correlates, but neural mechanisms of consciousness.

The panelists ended with questions from the audience, sparking a lively exchange ranging from issues of animal or artificial consciousness to criticism of the papers presented, to a clarification of terminology. Samet emphasized that although the "neural correlate of consciousness" may be useful, he was pessimistic about a satisfactory mechanistic account of conscious experience. Some audience members also questioned whether study of consciousness was premature at this point in our understanding of the brain. Myme countered, ending the discussion with the sentiment of "neurophilosopher" Patricia Churchland, that what today may seem mysterious and inscrutable is incrementally transformed into tomorrow's axiomatic understanding.