Brandeis University

Benjamin and Mae Volen National Center for Complex Systems

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The M.R. Bauer Foundation Colloquium Series, Distinguished Lecturer Series, and Symposium on Autism and Behavioral Genomics The M.R. Bauer Foundation Colloquium Series, Distinguished Lecturer Series, and Symposium on Autism and Behavioral Genomics 2003-04 Summary

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The past year (2003-04) represents a special milestone for the Volen National Center for Complex Svstems-its 10th anniversary. Almost from the beginning, the M.R. Bauer Foundation has supported the Bauer Colloquium Series and Retreat, later joined by the Bauer Distinguished Guest Lecturer Series, which have served to enrich the educational and research missions of the Center, raise its visibility in the neuroscience community, and strengthen connections between host and visitors. In light of this anniversary, I am especially pleased to present the proceedings of the 2003-04 M.R. Bauer Foundation Colloquium Series, Distinguished Guest Lecturer Series, and Symposium (Retreat) on Autism and Behavioral Genomics. My colleagues and I owe a special debt of gratitude to the M.R. Bauer Foundation for its continuous support that has enabled the Volen Center to mount these outstanding programs and advance the efforts of neuroscientists to understand the complex system constituted by the brain.

The **M.R. Bauer Colloquium Series** hosted seven speakers in 2003-04. The speakers focused on advances in understanding cellular and system changes that underlie learning and other behaviors, underscoring the link that is now commonly made by neuroscientists between physiological changes and behavior. **Denis Pare**, Ph.D., from Rutgers University talked about the physiological properties of certain neurons in the amygdala, which is thought to play a critical role in the expression and learning of fear responses. Disturbances in the amygdala are thought to be responsible for some human anxiety disorders, such as post-traumatic stress. Certain inhibitory neurons in this part of the brain are essential in reconciling the opposite requirements of plasticity and stability in brain networks. As these neurons are excited or depressed, there is an opposite change in the strength of inputs at other dendrites, leading to no net change in total synaptic weight despite a change in the relative strength of inputs.

Ann Graybiel, Ph.D., from MIT's McGovern Institute for Brain Research, reported on recordings made from the cortex of macaque monkeys as they executed a sequence of eye movements. Her surprising finding was that electrical activity in neurons peaked at the end of these movements, suggesting that this activity does not depend on sensory input but rather was an explicit signal inherent to the neuron marking the completion of learned behaviors.

Jonathan Cohen, Ph.D., from Princeton University spoke about one of the fundamental mysteries of neuroscience-how our capacity for purposeful behavior arises from the distributed activity of billions of neurons in the brain. Although we have a poor understanding of how systems in the brain lead to cognitive control (the ability to guide attention, thought, and action in accord with our intentions), he is using computational modeling to develop explanations for the function of particular brain systems. His work has led to novel hypotheses about how systems work in the brain as well as the discovery of new anatomic relationships.

Jeff Lichtman, Ph.D., from Washington University School of Medicine is taking advantage of new techniques to demonstrate the dramatic remodeling that occurs in brain circuits soon after birth. Using newly available techniques of genome manipulation and the fluorescent imaging of neurons that together permit scientists to label neurons with different colors so that synaptic circuitry can be untangled, he is showing how young mammals use experience to mold their nervous systems to conform to the world they inhabit.

Nelson Spruston, Ph.D., from Northwestern University described how sensory information is integrated in the hippocampus to provide a map of experience with a spatial component. He identified dendritic excitability, the spike in electrical activity at the connections between neurons, as the central factor in the process that leads to the formation of memories.

Todd Holmes, Ph.D., from New York University spoke about the interaction between biochemical signaling and electrical signaling as they influence neural circuits and animal behavior. He has engineered ion channels that have novel properties in order to determine how systematic changes in cellular electrical activity affect circadian rhythms, the physiology of neurons, and development. Michael Ehlers, Ph.D., from Duke University spoke about his work on the formation of receptors in the brain responsible for information storage. External stimuli trigger the strengthening of connections between neurons, growth in the number of receptors, and recycling of the materials used to create these receptors.

Now completing its sixth year, the M.R. Bauer Distinguished Guest Lecturer Series brought two outstanding neuroscientists to campus in 2004. David McCormick, Ph.D., serves as a professor of neurobiology at Yale University School of Medicine. He is best known for his work on the visual system, which has advanced our understanding of the forebrain (cortex) to a level that had previously been possible only with invertebrate systems. His public lecture, "The Possible Role of Recurrent Cortical Networks in Memory and Attention." emphasized that the brain is constantly active. During long periods of sleep and conscious attention, when there isn't any physical movement, cortical networks in the front of the brain generate persistent electrical activity through a balance of recurring excitation and inhibition. When this system is "unbalanced,' with electrical activity that is random or chaotic, the result is brain activity typical of epilepsy. With a stable network, changes in the excitability of neurons allow us to shift attention or remember something in a specific time and space.

McCormick indicated that there are two explanatory models for what is happening in the brain: (1) activity is generated through ion channel function in the membrane of neurons, or (2) activity is generated by the networks of neurons. It is more likely that networks are more important than membrane channels in controlling electrical activity that underlies our working memory, although membranes are clearly also involved in this process. He has discovered, for example, that H-channels, which serve as a pacemaker setting the heart rate, are also a major controlling factor in how much information gets to the central part of the neuron, and they may modulate neurons' ability to communicate. The brain is inundated with background activity. How does this recurrent electrical activity affect the connections between cells? This question may shed light on how we learn. Networks in the cortex are highly interconnected and highly plastic (i.e., they adapt to changes rapidly).

McCormick's hypothesis is that attentional command may select a subnetwork that enters into the "up" state, thereby biasing the processing of information. These mechanisms underlie our conscious focus on particular stimuli in the external world and permit our brain to filter the massive sensory and background information it receives. The stability of the neural network, balanced between electrical excitation and inhibition, allows the brain to shift focus rapidly, as needed. The other M.R. Bauer Distinguished Guest Lecturer was **Charles Zuker**, Ph.D., professor of biology and neurosciences at the University of California, San Diego, School of Medicine, as well as an Investigator of the Howard Hughes Medical Institute. Zuker was also the keynote speaker at the Volen National Center's 10th Anniversary Symposium on Autism and Behavioral Genomics, which served as this year's scientific retreat.

Zuker addressed "Signaling and Coding in the Mammalian Taste System: Sweet, Bitter, and Umami." For the past five years, he has been working to understand how the brain encodes and decodes sensory stimulations, particularly chemosensation in mammals. Before we can figure out how the brain does this, however, it is necessary to understand the process at the periphery, in other words, how taste cells work in the tongue.

The ability to discriminate tastes has important evolutionary implications for humans. For example, all toxins taste bitter to us, and lead to an aversion. Zuker concentrates on a family of genes that appear to be responsible for mediating the sweet and umami (amino acid) tastes. His genetic experiments are a striking example of how the selectivity for taste can be altered. Zuker validated in vivo that certain genes play an essential role in sensing sweetness. Humans like MSG 100 times more than any other amino acid, while mice like all amino acids equally. Unlike humans, mice do not like the taste of aspartame, an artificial sweetener, at all. These differences reflect the different ecological niches that humans and rodents occupy.

When the human receptor for sweetness is placed in a transgenic mouse, the mouse likes aspartame. There is a paradoxical complexity, however, underlying this simple sense. Zuker showed that we do not have broadly tuned cells but rather cells dedicated to each taste. Every taste cell expresses all 30 receptors (making them fundamentally different from olfaction cells). There is only one kind of "bitter" cell, however, that senses the full range of bitter tastes. "We need to know that something is bad," Zuker said, "but we don't need to know what kind of bad it is." He demonstrated through these experiments that we have a good grasp of how taste operates at the periphery (on the tongue).

But how is this information transferred to the brain? There do not appear to be broadly tuned areas across modalities in the brain. Taste is a property of the cell, not of the receptor. By elucidating the molecular genetics of taste, Zuker is working to demonstrate how the senses interact with the environment and how sensory information is processed in the brain. For animals, the attraction/ aversion response to each taste is a life-and-death issue. For humans, the inability to respond to certain features of the external environment appears to be at the heart of disorders such as autism.

The 2004 Volen Center retreat, the Symposium on Autism and Behavioral Genomics, sponsored in part by the M.R. Bauer Foundation, took place on the Brandeis campus on March 22. Seven speakers, including Zuker, helped to define, sometimes controversially, the progress that we have made in understanding one of the most elusive and troubling disorders of the brain. The Symposium was also one of the bestattended events in the Volen Center's history, with some 300 scientists, students, and interested lavpeople attending.

Edward Jones, Ph.D., director of the Center for Neuroscience at the University of California, Davis, describes a loss of connections in the brain as one of the underlying factors in schizophrenia. In the past two years, following the sequencing of the human genome, the search for susceptibility genes for schizophrenia has dominated the field. However, schizophrenia, like autism, is emerging as a complex disease whose origin is not a single process. These disorders share certain characteristics, including susceptibility genes and pre- and post-natal events that lead to circuitry in certain areas of the brain that, when faced with stresses in life, begin to decompensate, demonstrating a kind of maladaptive plasticity.

Leslie Griffith, Ph.D., from Brandeis University's Volen Center uses the biochemistry of fruit fly courtship behavior to illustrate how the brain forms memories and learns from the external environment in order to understand an important area of deficit in autism. Through a series of careful experiments, Griffith showed that associative courtship learning is mediated by a change in sensitivity to pheromones. The molecular basis of this change is a calcium-dependent protein that serves as the molecular switch for memory.

Thomas Insel, Ph.D., director of the National Institute of Mental Health, addressed the neurobiological basis of love and social affiliation. Using the prairie vole, a biparental species that forms pair bonds for life, he showed that some areas of the brain respond only to social information, and there are specific receptors and pathways in the brain for social attachments. Social behavior is a complex molecular system. Comparative studies of species of voles are beginning to shed light on the underlying mechanisms of social attachment, which in turn may offer potential ways to understand and treat autism.

Catherine Dulac, Ph.D., professor of molecular and cellular biology at Harvard University and a Howard Hughes Medical Institute Investigator, talked about the sensory coding of pheromone signals in the olfactory system. In rodents, pheromones are essential in parent-infant interactions. Because parent-infant interactions are also a key issue in autism, understanding the molecular basis of pheromone detection and processing may provide important insights in autism. Rudolph Jaenisch, Ph.D., from MIT's Whitehead Institute considered how cells are programmed for their roles and whether this programming was reversible. While cloning may possibly offer an intriguing way to reprogram cancer cells to reverse the disease, the process is too complicated at present to be successful or effective. He suggested that cloning might eventually provide clues both for understanding autism and treating it.

David Skuse, M.D., director of the Behavioral and Brain Sciences Unit of the Institute of Child Health at University College, London, spoke about the neurobiological basis of autism. Evidence suggests that autism is not a distinct condition but a spectrum of disorders that share certain features varying considerably in severity. Does mental retardation lower the threshold for trait manifestation in autism? Skuse believes it does, but he also points out that 75 percent or more of persons with autism have normal range IQs, a reversal of the current orthodoxy. With the need to redefine autism along a broader spectrum, Skuse also believes that the incidence of autism is more widespread than previously known. Autism is heritable, and it is probably related to less than 20 genes, with a distinctive neurobiological substrate. He has recently identified candidate genes that may be potentially associated with the development of social intelligence. Neuroscientists are close to piecing together, for the first time, a plausible explanation of how genetic variation affects social intelligence, which in turn would substantiate the biological origins of autism

In the past decade, the M.R. Bauer Foundation Colloquium and Scientific Retreat have served to facilitate the exchange of new knowledge, ideas, and techniques that together have advanced the study of the brain. memory, and learning. In the past six years, the M.R. Bauer Distinguished Guest Lecturer Series has brought an impressive list of some of the most outstanding neuroscientists in the world to the University. Both programs have greatly benefited our faculty and students through their contacts with the Bauer Colloquium speakers and Distinguished Guest Lecturers. These visitors, in turn, have encountered the exciting research and learning environments at the Volen Center and strengthened the web of collegiality that draws neuroscientists together in a common enterprise. This booklet represents an important part of the Volen Center's effort to reach out to neuroscientists in the international community in order to make this work more widely known and to continue these scientific discussions and collaborations. With sincere gratitude, I am pleased to recognize the support of the M.R. Bauer Foundation for making these programs possible through its foresight and generosity.

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

Denis Pare, Ph.D.

Department of Neuroscience Rutgers University Newark, New Jersey September 15, 2003

Physiological Properties of Intercalated Amygdala Neurons

This talk focuses on the amygdaloid complex, a nucleated structure of the temporal lobe. Much data suggests that the amygdala plays a critical role in the expression and learning of fear responses. Moreover, it is believed that disturbances in amygdala excitability are responsible for some human anxiety disorders, such as post-traumatic stress disorder. The amygdale is comprised of many nuclei. I will focus on two of them: the basolateral and central nuclei. The basolateral group receives sensory afferents and projects to the central nucleus, the main source of amygdale projections to brainstem nuclei mediating fear responses. Thus, the basolateral and central nuclei are seen as the input and output stations of the amygdale, respectively.

The work I present examines how transmission of sensory inputs from the basolateral group to the central nucleus is regulated by a group of inhibitory neurons, known as the intercalated cell masses. Intercalated neurons receive excitatory inputs from the basolateral group and in turn inhibit neurons of the central nucleus. However, because intercalated neurons are interconnected, the amount of inhibition they generate in the central nucleus depends on the timing and nature of sensory inputs. As a result, the behavioral consequence of sensory events will vary. I also describe experiments indicating that intercalated neurons express a form of short-term memory inscribed in their intrinsic membrane properties. I show that intercalated neurons express an unusual potassium current that causes them to modify their excitability as a function of their recent activity.

The final section of my talk focuses on mechanisms of synaptic plasticity that is how the brain stores information. Memory is believed to depend on activity-dependent changes in the strength of synapses. In part, this view is based on evidence that the efficacy of synapses can be enhanced or depressed depending on the timing of pre- and postsynaptic activity. However, when such plastic synapses are incorporated in neural network models, stability problems develop because the potentiation or depression of synapses increases the likelihood that they will be further strengthened or weakened. I describe biological evidence for a homeostatic mechanism that reconciles the apparently opposite requirements of plasticity and stability. I show that in intercalated neurons, activitydependent potentiation or depression of particular inputs leads to opposite changes in the strength of inputs ending at other dendritic sites. As a result, no net change in total synaptic weight occurs even though the relative strength of inputs is modified. Thus, in intercalated neurons at least, the total weight of plastic synapses is conserved by inverse homo vs. heterosynaptic modifications.

Ann Graybiel, Ph.D.

Department of Brain and Cognitive Sciences McGovern Institute for Brain Research at Massachusetts Institute of Technology Cambridge, Massachusetts September 29, 2003

Learning and Memory Mechanisms in the Basal Ganglia: Plasticity in Basal Ganglia Loops

Complex biological systems such as human language and the genetic code are characterized by explicit markers at the beginning and end of functional sequences. We have recorded the macaque prefrontal cortex while the monkey executes a sequence of cued saccades. The surprising finding is that some neurons show a phasic peak of spike activity marking the endpoint of the series of saccades. Variation in many of the properties of the stimulus indicated that the peak was not sensory driven and did not depend on any kind of rhythmicity of stimulus presentation. We conclude that neurons carry an explicit signal that marks the completed performance of learned behaviors.

Jonathan D. Cohen, Ph.D.

Department of Psychology Princeton University Princeton, New Jersey October 27, 2003

Computational Modeling of Neural Mechanisms Underlying Cognitive Control

Cognitive control is the ability to guide attention, thought, and action in accord with goals or intentions. One of the fundamental mysteries of neuroscience is how this capacity for coordinated, purposeful behavior arises from the distributed activity of many billions of neurons in the brain. Several decades of cognitive and neuroscientific research have focused on the mechanisms by which control influences processing (e.g., attentional effects in sensory processing, goal-directed sequencing of motor output, etc.), and the brain structures upon which these functions depend, such as the prefrontal cortex, anterior cingulate cortex, basal ganglia, and brainstem neuromodulatory systems. However, we still have a poor understanding of how these systems give rise to cognitive control. Our work seeks to develop formally explicit hypotheses about the functioning of these systems, and to test these hypotheses in empirical studies. An important motivation for this work is the development of a theoretically sound foundation for research on the relationship between disturbances of brain function and their manifestation as disorders of thought and behavior in psychiatric illness.

Neural network models are developed as a way of articulating precise hypotheses about the function of particular brain systems, and their role in cognitive control. This work seeks to bridge the traditionally disparate levels of analysis of neurophysiology, systems neuroscience, and cognitive psychology. Projects focus on the function of systems considered to be critical for cognitive control, including (a) the role of prefrontal cortex in biasing attention and response selection in posterior structures; (b) the

Jeff Lichtman, Ph.D.

Department of Anatomy and Neurobiology Washington University School of Medicine St. Louis, Missouri November 3, 2003

Monitoring Synaptic Competition in Fluorescent Mice

At the end of the 19th century, Ramon v Cajal's application of the Golgi method revolutionized neurobiology by showing that the neuron is the brain's organizational unit. For most of the 20th century, Cajal's wonderful drawings and analysis remained the last word on the cellular organization of many regions of the adult and developing brain. However, all this is changing due to the convergence of two new sets of technical developments. First are the methods of genome manipulation that have made it possible to insert genes from jellyfish and other aquatic creatures that encode fluorescent proteins stably into lines of transgenic mice that express these fluorescent proteins in the brain. Second is the development of a suite of confocal, multi-photon, low-intensity, and computational methods that allow imaging of fluorescent neurons in living animals at a resolution previously obtainable only in thin sections of fixed tissue. Together, these methods now make it possible to label different neurons in different colors so that synaptic circuitry can be untangled. Moreover, it is now possible to view neurons in living animals so that the same individual cells and synapses can be monitored over minutes or months as they change in response to experience, aging or disease. Perhaps the most exciting use of such transgenic animals is that they provide the first way to assay the cellular alterations that underlie behavioral changes such as memory formation.

My colleagues and I have used such transgenic fluorescent mice to monitor a dramatic remodeling of synaptic circuits that takes place in early postnatal life in mammals. This

role of brainstem dopamine systems in regulating learning and updating of representations in prefrontal cortex; (c) the role of the anterior cingulate cortex in monitoring performance, and its influence on adaptations in control; and (d) the influence of locus coeruleus and norepinephrine on attentional state. In many cases, modeling work has led to novel predictions about neurophysiolgical mechanisms underlying systems-level function, such as: (a) gain control as a mechanism for dopaminergic neuromodulation; (b) the role of dopamine in coordinating reinforcement learning and the gating of information into prefrontal cortex; (c) the influence of electrotonic coupling on population dynamics within the locus coeruleus; and (d) the effects of changes in locus coeruleus physiological state on attentional mode. In other cases, this work has led to novel hypotheses about system level function, such as the response of anterior cingulate cortex to conflict in processing and its influence on adaptive changes in cognitive control. This work has also predicted, and led to the discovery of, new anatomic relationships, such as projections from the anterior cingulate cortex to locus coeruleus.

Nelson Spruston, Ph.D.

Department of Neurobiology and Physiology Northwestern University Evanston, Illinois February 3, 2004

Dendritic Integration in Hippocampal Pyramidal Neurons

In the hippocampus, sensory information is integrated to provide a contextual map of experience with a strong spatial component. In addition, the hippocampus is a crucial structure for the formation of new declarative memories (including spatial memory). In my laboratory, we study the cellular processes that allow hippocampal neurons to carry out these functions and to change their function as a consequence of experience.

Research in my lab focuses on the excitable properties of CA1 dendrites and their role in synaptic integration. Dendritic excitability is likely to be a central factor in the process of synaptic integration, as well as in mediating activity-dependent plasticity that may be responsible for the function of the hippocampus during learning.

remodeling likely plays a critical part in the way young mammals use experience to mold their nervous systems to conform to the world they live in. We have focused on a particularly accessible system, the connections between spinal motor neurons and muscle fibers. In adults each muscle fiber is innervated by exactly one motor neuron and at just one site, the neuromuscular junction. Each motor neuron, however, distributes its innervation to a number of muscle fibers. A "motor unit" is the distributed subset of the muscle fibers in a muscle that are exclusively activated by one neuron. In rodents this pattern emerges in early postnatal life by the sorting of connections of different motor neurons that initially overlap at multiple innervated neuromuscular junctions. By time-lapse imaging in vivo in animals bred such that different axons express different colored fluorescent proteins, we have begun to directly observe the way neuromuscular junctions undergo the transition from multiple to single innervation and motor units become non-overlapping. These studies reveal a massive change in connectivity during early postnatal life that appears to be driven by a highly dynamic competition between axons that transiently co-occupy the same synaptic sites.

Todd Holmes, Ph.D.

Department of Biology New York University New York, New York February 23, 2004

Circuit-Bashing (and repair) by Transgenic Manipulation of Neural Electrical Excitability

My major interest is the interaction between biochemical signaling and electrical signaling as they influence neuronal circuits and animal behavior. Ionic flux across cell membranes is mediated by ion channel membrane proteins. The activity of membrane ion channels is highly plastic; their activity is regulated by a wide range of biochemical signaling molecules, including protein kinases. My laboratory is focused on unraveling the molecular mechanisms of ion channel regulation, and the physiological consequences of this regulation. Recently, we have begun to engineer ion channels that exhibit novel regulatory properties. These modified ion channels are being introduced into transgenic animals in order to determine how systematic changes in cellular electrical activity determine circadian behavior, neuronal physiology, and development.

My interests in protein engineering and neurobiology extend to studies of peptide-based biomaterials. I have identified a unique class of biomaterials that mimics many of the features of extracellular matrix. These materials are being developed to serve as artificial scaffolds for tissue engineering and transplantation.

Michael D. Ehlers, Ph.D.

Department of Neurobiology Duke University Durham, North Carolina May 17, 2004

Recycling Endosomes, Nonconventional Receptors, and Plasticity Mechanisms at Glutamatergic Synapses

Long-term potentiation (LTP) of synaptic strength, the most established cellular model of information storage in the brain, is expressed by an increase in the number of postsynaptic AMPA receptors. However, the source of AMPA receptors mobilized during LTP is unknown. We have demonstrated that transport from recycling endosomes to the plasma membrane maintains the supply of AMPA receptors at excitatory synapses and is required for LTP. Surprisingly, stimuli which trigger LTP, promote not only AMPA receptor insertion, but also generalized recycling of cargo and membrane from endocytic compartments. These results identify recycling endosomes as the source of AMPA receptors for LTP, and provide an unexpected mechanistic link between synaptic potentiation and membrane remodeling during synapse modification.

A key step in glutamatergic synapse maturation is the replacement of postnatally expressed N-methyl-Daspartate receptors (NMDARs) with mature forms which differ in subunit composition, stably attach to synaptic sites, and are thought to "solidify" neural circuitry. However, the mechanisms underlying the removal and replacement of synaptic NMDARs are poorly understood. We have demonstrated that NMDARs containing the developmentally regulated NR3A subunit undergo rapid endocytosis from the dendritic plasma membrane. This endocytic removal is controlled by the adaptor protein PACSIN1/

syndapin1, which directly binds the carboxy-terminal domain of NR3A through its NPF motifs and assembles a complex of proteins including dynamin and clathrin. Endocytosis of NR3A by PACSIN1 is activity-dependent, and disruption of PACSIN1 function causes NR3A accumulation at synaptic sites. Our results reveal a novel, activitydependent mechanism involved in the regulation of NMDAR expression at synapses during development, and identify an adaptor that confers spatiotemporal and subunit specificity to NMDAR endocytosis.

The M.R. Bauer Distinguished Lecturer Series Summaries 2003-04

Introduction

One of the highlights again this year has been the M.R. Bauer Distinguished Guest Lecturer Series. This program, now in its sixth year, brought to campus two outstanding people, both well-known neuroscientists—Charles Zuker, professor at University of California, San Diego, and Howard Hughes Medical Institute Investigator, and David McCormick, professor of Neurobiology at Yale University.

Both guests spent a week at Brandeis. Charles Zuker was the keynote speaker of the Symposium on Autism and Behavioral Genomics. Zuker and McCormick's schedules were full with a public lecture, class sessions, presentations at journal clubs, meetings with graduate students and postdoctoral fellows, and spending time in many neuroscience laboratories. Feedback from our students indicates that it is a significant privilege to have had 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.

Charles Zuker, Ph.D.

University of California, San Diego Howard Hughes Medical Institute Investigator San Diego, California March 22, 2004

Signaling and coding in the Mammalian Taste System: Sweet, Bitter, and Umami

Mammals can detect sweet, bitter, sour, salty, and umami (roughly speaking, amino acid) stimuli. The ability to discriminate between such stimuli underlies our ability to avoid noxious substances while recognizing sources of high-caloric or nutrient-rich food. The Zuker lab is currently interested in answering basic questions about the detection of taste signals, focusing on the isolation and characterization of genes encoding sweet, bitter, and umami taste receptors. The process of identifying proteins that may function as taste receptors proves a powerful molecular tool to investigate not only the function of taste receptor cells but also the logic of taste coding, allowing us to ask questions such as: How is tastant specificity and taste discrimination accomplished at the periphery? What is the topographic organization of sweet, bitter, and umami cells on the tongue? How is the information transmitted and encoded in the afferent nerves?

In association with Nick Ryba at the NIDCR, Zuker's lab has been carrying out a comprehensive molecular and genetic dissection of taste transduction in mammalian model systems. Initially, they isolated two novel families of taste receptors expressed in subsets of taste receptor cells of the tongue and palate. One of these, the T2Rs, encompasses ~30 different genes that they feel encode mammalian bitter taste receptors. The other family, the T1Rs, contains three members that combine to function as the mammalian sweet (T1R2+3) and amino acid (T1R1+3) taste receptors.

These discoveries suggest that the taste of bitter, sweet, and umami may be transduced by "labeled lines"-separate, independent pathways-in the periphery of the taste system. Indeed, receptors for each quality appear, in Zuker's hands, to be expressed in distinct populations of taste cells. The entire family of bitter receptors get coexpressed in all bitter-receptive taste cells, which are entirely distinct from the taste cells expressing sweet or umami receptors. Various imaging and electrophysiological experiments have confirmed that cells containing one of these receptors (or receptor families) respond only to ligands (i.e., taste compounds) with the appropriate overall taste quality.

An important question, however, arises when attempting to connect these facts with the physiology of perception: are the T2R receptors truly involved in faithfully transmitting information about bitter tastes, and only bitter tastes? Relatedly, are the other identified receptors specifically related to transmission of information about sweet or umami taste? The researchers in Zuker's lab have used genetic engineering techniques to prepare mutant mice that lack particular proteins—or particular parts of the posttransduction cascade-and in so doing have provided evidence in favor of this hypothesis. First, they prepared mice lacking PLC≤2, a phospholipase that lies downstream of the bitter, sweet, and umami receptors. These mice proved to prefer all tastants equally to water. suggesting that they are insensitive to the specific qualities of sweet, bitter, and umami tastes. They then produced new mutant mice in which PLC≤2 function was rescued in subsets of cells expressing only one or another receptor; the mice then preferred that particular taste quality to the same degree as normal mice (e.g., preferring sweet and rejecting bitter in a concentration-dependent fashion). Importantly, the mutant mice with a particular rescued receptor not only responded normally to that particular tastant, but continued to appear insensate to other tastes.

Most recently, Zuker and colleagues engineered mice in which a nontaste receptor-a modified º-opioid receptor that transduces a synthetic ligand never experienced by normal mice-was expressed only in cells expressing T1R2, sweet-responsive cells. These mice preferred the synthetic ligand, which they normally ignore, similarly to other sweeteners. This suggests that any chemical transduced by cells expressing sweet receptors essentially tastes sweet to the mice, further supporting the idea that sweet is coded peripherally by a labeled line.

Future work in the Zuker lab will attempt to extend this last result to bitter receptors, and to search for other receptors—the receptor for sour, for instance. Recent advances in molecular genetics will be used to extend Zuker's analysis of taste coding to central processing stations, as well. This bottom-up approach will allow him to examine the degree to which the putative labeled-line processing of taste stimuli can be extended into the central nervous system.

David McCormick, Ph.D.

Department of Neurobiology Yale University New Haven, Connecticut June 1, 2004

Possible Role of Recurrent Cortical Networks in Memory and Attention

The cerebral cortex is a sheet of neurons, approximately the size of a small pizza, and about the thickness of the cardboard underneath. It is massively interconnected, vertically and especially horizontally. Neurons of the cerebral cortex have a resting membrane potential, in the lack of synaptic inputs, approximately 20 mV away from firing threshold. We hypothesize that the ongoing, spontaneous activity of the cortex provides the bulk of this 20 mV of depolarization needed to get the cell near firing threshold. Thus, the recurrent connectivity of the cortex is built so that much of the 10,000 to 30,000 synaptic inputs provide a context within which the cell operates.

That context, generated largely through recurrent network activity in the cortex, rapidly controls neuronal excitability and functional connectivity, allowing for the functional grouping and ungrouping of cortical neuronal networks in a manner necessary for behavior. Two examples of the utility of these functional networks are those of working memory and selective attention. Working memory allows one to keep in mind features of an ongoing task, putting together sequences into a logical whole. Neuronal networks in the prefrontal cortex exhibit persistent activity that is correlated with working memory. In attention, neuronal responsiveness rapidly increases and decreases with attention/ inattention. What are the mechanisms by which neuronal activity and responsiveness may be rapidly regulated within the cerebral cortex?

Our research has focused on the ability of local networks within the cerebral cortex to, either spontaneously, or in response to activation of an afferent input, generate rapid changes in neuronal activity and responsiveness through recurrent network activity. During anesthesia and slow wave sleep, this recurrent network activity is generated by a fine balance between local feedback excitatory and inhibitory loops. The activation of these loops results in a relatively stable state in cortical networks, such that the neurons are poised near firing threshold and spontaneously active in what is termed an UP state. We suggest that a basic operating principle of the cerebral cortex in the waking animal is the rapid and dynamic reconfiguration of functional networks based upon the selection and activation of recurrent networks of cells, in a manner similar to the generation of UP states during sleep and anesthesia. In this manner, the ongoing activity of the large cortical sheet may provide the behavioral and intellectual context to each cell and local network needed to provide appropriate responsiveness. This hypothesis is currently being thoroughly examined and tested.

The 2004 Volen National Center for Complex Systems and Biology Symposium on Autism and Behavioral Genomics

The Brandeis University Symposium on "Autism and Behavioral Genomics" was sponsored by the Nancy Lurie Marks Family Foundation and the M.R. Bauer Foundation. The symposium, which took place on March 22, 2004, was held at the Spingold Theater at Brandeis, and was in celebration of the grand opening of the National Center for Behavioral Genomics and the 10th Anniversary of the Volen National Center for Complex Systems.

Symposium on Autism and Behavioral Genomics

Monday, March 22, 2004 8:45 am-5:00 pm Spingold Theater

Morning Session

8:45 am Welcoming Remarks

9:00 am Keynote Speaker Charles Zuker, Ph.D. "Signaling and Coding in the Mammalian Taste System: Sweet, Bitter, and Umami" Professor University of California, San Diego Howard Hughes Medical Institute Investigator

9:45 am Edward Jones, Ph.D. "Defining the Neuronal Phenotype in Major Mental Disorders" Director Center for Neuroscience University of California, Davis

10:30 am Break

11:00 am Leslie Griffith, Ph.D. "Sex and the Single Fruit Fly: Courtship Behavior and Learning" Associate Professor of Biology Volen National Center for Complex Systems Brandeis University

11:45 am Thomas R. Insel, Ph.D. "Social Neuroscience: From Genes to Behavior" Director National Institute of Mental Health

12:30 pm Lunch Sherman Function Hall

Afternoon Session

2:00 pm

Catherine Dulac, Ph.D. "Molecular Architecture of Pheromone Sensing in Mammals" Professor of Molecular and Cellular Biology Harvard University

2:45 pm

Rudolph Jaenisch, Ph.D. "Epigenetic Regulation in Development and Disease" Professor of Biology Massachusetts Institute of Technology Whitehead Institute for Biomedical Research

3:30 pm Break

4:00 pm David H. Skuse, M.D., FRCP, FRCPsych, FRCPCH "The Neurobiological Basis of Autistic Disorders: Myths and Prospects" Director of Behavioral and Brain Sciences Research Unit Institute of Child Health University College, London

4:45 pm Closing Remarks

Edward Jones, Ph.D.

Director Center for Neuroscience University of California, Davis Davis, California March 22, 2004

Defining the Neuronal Phenotype in Major Mental Disorders

Schizophrenia affects 1% of the world's population independent of race, culture, or socio-economic status, with enormous social and economic consequences. Depression is even more common with an overall incidence of about 19%. The incidence of both disorders increases substantially in close relatives reaching a concordance of at least 50% in monozygotic twins. This indicates a strong genetic element but also the possibility that epigenetic factors may also play a role. There is some evidence that these factors may operate during brain development.

Neuropathological studies have ruled out the likelihood of a progressive degeneration, an overt pathology of a single cell type, and overt localization of pathology to a single brain region. In schizophrenia dilatation of the lateral ventricles and hypoactivity of the dorsolateral prefrontal cortex suggest a defect of brain circuitry that is supported by the loss of thalamocortical neurons in the mediodorsal nucleus of the thalamus, by cellular changes within the cortex itself, and by manifestations of activity-dependent up and down regulation in genes sensitive to changes in neural activity.

Linkage, association, and gene profiling studies have identified numerous genes that may confer susceptibility to schizophrenia and depressive illness. These affect a wide variety of brain mechanisms including neural transmission, myelination, and metabolic processes. Of the first mentioned, the putatively involved genes could operate at presynaptic, postsynaptic sites or further downstream with influences upon neuronal signaling and gene transcription. High throughput expression profiling of large cohorts of human brain tissue in schizophrenia and depression points to a wide variety of possible susceptibility genes whose involvement remains to be verified. The image of these diseases that is emerging suggests the existence of genes that confer susceptibility that are acted upon by epigenetic factors during development and maturation of the nervous system and in which the disease process, by engaging brain mechanisms of plasticity, may itself play a role in establishing the definitive neuronal phenotype of each disorder.

Leslie Griffith, Ph.D.

Volen National Center for Complex Systems Brandeis University Waltham, Massachusetts March 22, 2004

Sex and the Single Fruit Fly: Courtship Behavior and Learning

Humans have about 35,000 genes and fruit flies about 13,000, with about 60 percent of the fruit fly's genes having a human homologue. Many of these genes conserve ancient behaviors, including courtship. I have defined two kinds of learning-non-associative learning, which is when the animal learns about a particular stimulus and associative learning, which is a more complicated process. Fruit fly courtship behavior appears to be stereotyped, with a pattern that includes the following: tapping, wing extension, the courtship song, licking, and copulation. But the fly's courtship behavior is also plastic. Associative learning for courtship, prompted by pheromones for either stimulation or aversion, can last between hours and days. How does learning alter behavior? I have noted an increased latency or lag-time between flies' meeting and the commencement of courting. Through a series of careful experiments, I show that associative courtship learning is mediated by a change in sensitivity to pheromones. What is the molecular basis of the change? The calcium-dependent protein kinase CamKII serves as the molecular switch. Acute inhibition of this enzyme blocks learning and memory, while increasing enzyme actions was shown to enhance the fly's response during training. This enzyme is critical for setting sensory thresholds in pheromone-driven learning in fruit flies. Understanding how the brain forms memories and learns from the external environment will help scientists pinpoint what goes wrong in autism.

Thomas R. Insel, Ph.D.

Director National Institute of Mental Health Bethesda, Maryland March 22, 2004

Social Neuroscience: From Genes to Behavior

One of the most challenging questions for our understanding of the brain is how this complex organ of a few billion cells manages complex functions such as language, emotion, and consciousness. This presentation takes on the seemingly impossible task of trying to understand the brain mechanisms for complex behavior, specifically social attachment (which, in humans, we call "love"). This task becomes tractable because of two insights. First, there are many mammals (besides humans), which form long-term social attachments. Our studies have focused on prairie voles, a monogamous rodent. The second insight is that a family of neuropeptides, including oxytocin and vasopressin, seems to have an important role in social behavior across evolution.

Vasopressin and oxytocin appear to be critical for the development of a long-term selective social bond in prairie voles. Under natural conditions, prairie voles form bonds only after mating. If oxytocin or vasopressin is given in the absence of mating, the voles will bond. More important, if prairie voles mate but are treated with a blocker of oxytocin or vasopressin, they fail to bond. Thus, it appears that these neuropeptides, normally released with mating, are necessary and sufficient for pair bonding. What is intriguing is that these neuropeptides have no such effect in other species of voles that are not monogamous. Prairie voles, as well as other monogamous species, have a unique distribution of brain receptors for oxytocin and vasopressin, such that these neuropeptides can influence reward pathways in the

Catherine Dulac, Ph.D.

Department of Molecular and Cellular Biology Harvard University Cambridge, Massachusetts March 22, 2004

Molecular Architecture of Pheromone Sensing in Mammals

The neuronal processing of pheromone signals within distinctive brain structures leads to marked changes in animal behavior and endocrine status. The highly reproducible and species-specific character of the response to pheromones offers a unique opportunity to uncover the neural basis of genetically pre-programmed behaviors.

Basic mechanisms of pheromone detection have been identified in a variety of animal species. We review recent investigations into molecular and neuronal sensory processing in the mouse, which have revealed a sensory strategy that is strikingly different from that of other chemosensory modalities such as taste and olfaction. These studies have provided novel insights into the sensory coding of pheromone signals leading to gender identification and aggressive behavior, and into the developmental mechanisms leading to the emergence of distinct olfactory pathways.

brains of monogamous species. The mechanism for these striking species differences in receptor distribution is not entirely clear, but may be related to a variation in the sequence of the regulatory part of the genes for these receptors. Engineering the mouse genome to induce a prairie-vole like pattern of receptors results in an increase in social behavior in response to vasopressin.

One implication of these results involves autism, a neurodevelopment disorder characterized by a reduction in social behavior and abnormal social attachment. There are reports of reduced oxytocin in children with autism. Perhaps more important is a recent finding that the same genetic region which discriminates monogamous from nonmonogamous voles also appears to show variation in the human genome and that one version of this region is transmitted at a high rate in children with autism. We do not know yet whether the autistic brain has an altered distribution of vasopressin or oxytocin receptors. Nevertheless, a principle elucidated from the vole studies-that the confluence of oxytocin or vasopressin circuits with the brain's reward pathways is critical for social attachmentdeserves careful study in autism.

Rudolph Jaenisch, Ph.D.

Professor of Biology Massachusetts Institute of Technology and Whitehead Institute for Biomedical Research Cambridge, Massachusetts March 22, 2004

Epigenetic Regulation in Development and Disease

The full term development of sheep, cows, goats, pigs, and mice has been achieved through the transfer of somatic cell nuclei into enucleated oocytes. However, only a small percentage of conceptuses survive to term and are characterized by high mortality rate and widespread epigenetic abnormalities due to misexpression of many genes. We are using nuclear transplantation procedures to compare the potency of stem cells, differentiated cells and of transformed cells to direct embryonic development.

Nuclear cloning represents a general and unbiased approach to probe whether cellular differentiation involves epigenetic as opposed to genetic alterations. The utility of the approach was demonstrated by the generation of monoclonal mice from mature B and T cells demonstrating that the genetic alterations that occurred in a single donor cell, i.e., the somatic rearrangements of the IgG and TCR loci, could be amplified and were present in all tissues of the monoclonal mice. Following a similar logic we used the nuclear transfer procedure to assess whether irreversible alterations occur during the maturation of cortical or olfactory neurons and could be visualized in a cloned animal. Only one allele of about 1,500 receptor genes is expressed in a given olfactory neuron but the mechanism of receptor choice and monoallelic expression is obscure. We have derived cloned mice from mature olfactory neurons that expressed the P2 olfactory receptor. The analysis of the cloned mice suggest that neuronal maturation and olfactory receptor choice does not involve genetic alterations that would interfere with

nuclear potency to generate mice. Our results also indicate that receptor choice in olfactory neurons is fully reversible.

The malignant state of tumor cells is known to be caused by genetic as well as epigenetic changes of the genome, prompting us to use nuclear transfer as an approach to distinguish between these changes. As nuclear donors we are using embryonic carcinoma cells and somatic cancer cells, including leukemia cells and solid tumors such as melanoma cells. Our results suggest that the genome of some somatic cancer cells can be reprogrammed to direct at least some embryonic development after transfer of the nucleus into the oocvte indicating that the tumor phenotype is largely determined by epigenetic alterations. In contrast, when we derived ES cells by nuclear cloning from embryonic carcinoma (EC) donor cells, we did not observe a gain in developmental potency suggesting that genetic rather than epigenetic changes are responsible for the phenotype of EC cells.

David H. Skuse, Ph.D.

M.D., FRCP, FRCPsych, FRCPCH Director of Behavioral and Brain Sciences Research Unit Institute of Child Health London, United Kingdom March 22, 2004

The Neurobiological Basis of Austistic Disorders: Myths and Prospects

Increasing evidence suggests that autism is not a distinct condition but a spectrum of disorders, which have in common features that vary considerably in severity. The shape and nature of the boundaries of this "autistic spectrum" are unclear. Recent research indicates that autistic disorders are caused indirectly by complex genetic influences. Genes are nondeterministic risk factors, and a genetic predisposition- which could be guite common in the general population-does not necessarily manifest in overtly autistic behaviors.

The following are timely and critical questions about the origins of autism:

•What have we learned about genes that influence the risk of developing autism?

•How does genetic risk influence the functioning of the brain?

•What correspondence is there between abnormal brain functioning and observable autistic behaviors?

•Why doesn't everyone at genetic risk of autism become autistic?

Gene discovery could be helped by two novel and complimentary approaches:

•First, developing dimensional measures that can sensitively capture the severity of autistic behaviors—no single component of which is qualitatively distinct from normal behavior.

•Second, discovering endophenotypes for autism, which are subtle physiological or psychological abnormalities that directly reflect genetic susceptibility, but which are often not associated with overt behavioral disorder.

Progress in understanding the genetic risks associated with autistic disorders has largely proceeded on the assumption that a small number of genes is involved, and that affected members of the same family share the same genetic risk.

Complementary investigations have assessed the role played by rare and severe genetic anomalies in isolated individuals or families. Neither approach has made direct links between the nature of the genetic risk and abnormal functioning of the autistic brain. Yet remarkable and consistent findings are now being made that indicate the nature of functional anomalies in the brains of autistic people. A primary impairment lies in social intelligence, reflected in the processing of social and emotional information. This deficit is associated with some structural brain anomalies but, more particularly, with abnormal activation of regions collectively known as "the social brain."

Our previous work suggests specific genes on the X-chromosome, which are expressed differently in males and females, lower the threshold for the overt expression of genetic vulnerability to autism conferred by genes elsewhere on the genome. In collaboration with colleagues at the Whitehead Center for Genome Research at MIT, we have recently identified candidate genes that are potentially associated with the development of social intelligence, because of their influence on the functional integrity of the social brain. We are close to piecing together, for the first time, a plausible picture of how genetic variation influences social intelligence, thereby illuminating the biological origins of the autistic disorders.

The text of this summary of the Bauer Foundation series, along with summaries from previous years, can be found at: www.bio.brandeis.edu/ bauer/previous.html.

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