Brandeis University

Benjamin and Mae Volen National Center for Complex Systems

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

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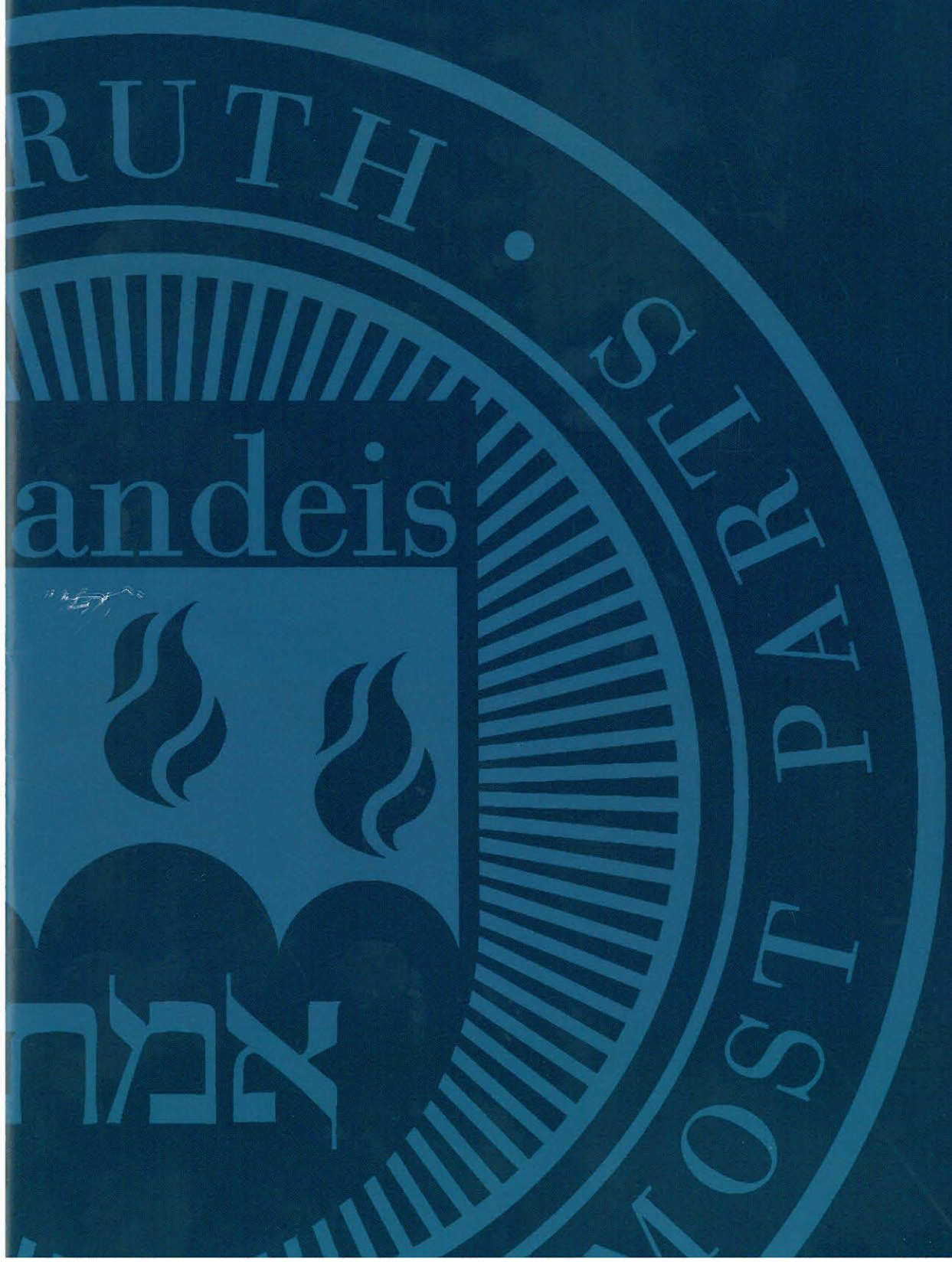

The M.R. Bauer Foundation Colloquium Series, Distinguished Lecturer Series, and Scientific Retreat 2009–2010 Summary

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The 2009–2010 M.R. Bauer Foundation Colloquium Series, Distinguished Guest Lecturer Series and Annual Scientific Retreat

Introduction

Neuroscience is a new science, although its underlying interests have been perennial ones. Over 2,000 years ago Aristotle taught that the mind, or intellect, must be unmixed with the body. This is so, he reasoned, because the mind can think about objects of any sort (in contrast to the sense organs, whose functions are limited to a single modality). Five hundred years ago, Descartes argued that the brain and mind, while intimately connected (as he thought, through the pineal gland), are separate and distinct entities. That the mind is embodied in a brain—that to understand the workings of the mind, we must understand the workings of the brain—is a relatively recent insight. This insight brings together biological disciplines with psychological ones in a common scientific pursuit—and it has been, since its inception, the animating purpose of the Volen National Center for Complex Systems at Brandeis University.

More than a decade ago, the Volen Center entered into a fruitful partnership with the M.R. Bauer Foundation. Support from the Bauer Foundation makes possible two annual series, the M.R. Bauer Colloquium Series and the M.R. Bauer Distinguished Guest Lecturer Series, as well as an annual scientific retreat.

Interdisciplinary discussion is the hallmark of each of these programs. They are founded on the recognition that neuroscience exists and flourishes at the intersection of neurobiology, computation modeling, cognitive science and other fields.

The fruits of these scientific exchanges can be seen in these proceedings. The talks summarized here range widely in their specific topics and findings. Yet a common theme runs through them: the extraordinary richness, complexity and subtlety of the connections by which the nervous system operates. This is evident in the normal functioning of healthy organisms, and it is also evident in the unfortunate breakdown of that functioning through illness or malformation. Studying these connections not only deepens our understanding of the workings of the brain, it also holds the promise of progress in treatment of diseases of the central nervous system.

Like other scientific fields, neuroscience is a collective enterprise and a continuing one. Neuroscientists build on the work of colleagues and predecessors, and, in turn, train and mentor the next generation of scientists. The M.R. Bauer Colloquium Series, Distinguished Guest Lecturer Series and Scientific Retreat are integral parts of this process. At each of these events, senior scientists and junior colleagues come together with postdoctoral fellows and graduate students. They exchange new knowledge. They air new ideas. New collaborations begin to take shape. This is how the field moves forward.

The publication of these proceedings further widens the conversation. Through these proceedings, we extend to the larger community of neuroscientists the insights and findings of each of the speakers in the M.R. Bauer programs at the Volen Center. We are grateful for the generous support that makes all of this possible, and we are honored by this long-standing association.

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

The M.R. Bauer Colloquium Series Summaries

Introduction

When we think of networks in the 21st century, a range of social and professional networking tools are often the first things that come to mind. Websites such as LinkedIn, Facebook, YouTube and Twitter have revolutionized the way we communicate, allowing us to reach out to our communities, locally and globally, forever changing the flow and access of information and ideas. Utilization of a network to achieve a higher level of organization, efficiency and communication, however, is not a concept unique to the recent technological age. From signaling cascades within a single brain cell (neuron), to the complex inner-workings of the human brain, networks can be observed in almost every aspect of nature, and they provide much of the framework for our modern understanding of complex cognitive processes and their biological underpinnings.

The 2009–2010 M.R. Bauer Foundation Colloquium Series focused on the theme "networks," representing networks in several senses. First, the proper establishment of connections within a biological network is critical to the function of the network as a whole. Second, just as the environment an organism encounters is constantly changing, so too must the connections within a network be remodeled according to the given needs of a situation. And finally, the M.R. Bauer Foundation Colloquium Series itself represents a "network" for Brandeis Volen Center neuroscientists and their guests to meet together to discuss, to learn from each other and to hypothesize about important scientific topics.

The guest speakers this year included experts from diverse fields within neurobiology, including synaptic plasticity, sensory perception, synapse development and cell identity. We begin our 2009–2010 report with summaries of the presentations of six distinguished scientists who made up this year's M.R. Bauer Colloquium Series. In presenting these summaries we have ordered them by the emerging picture they build, from nervous system plasticity (du Lac) to networks underlying cognition and potential dysfunction (Balice-Gordon). It is our pleasure to bring them to you.

Sascha du Lac, Ph.D.
Associate Professor
Systems Neurobiology Laboratories
Salk Institute for Biological Studies and
Investigator, Howard Hughes
Medical Institute
Feb. 22, 2010

Stability and Plasticity in the Sense of Balance

Because the world we live in is always changing, so too must an organism be able to adapt its behavior according to the demands of a given situation. The du Lac lab at the Salk Institute in California examines the impact our balance has on maintaining visual acuity while we are in motion. Disruptions in this network are thought to underlie a variety of vestibular disorders that cause debilitating dizziness in a large number of older adults.

Research in the du Lac Lab focuses on the neuronal mechanisms of learning. Our ability to see clearly while we move depends critically on eye movements that stabilize images on the retina of the eye during self-motion. Specialized movement detectors in the inner ear convey information to the brain about the direction and speed of the motion of our head via the vestibular nerves. Neural circuits in the brainstem and cerebellum transform these motion signals into motor commands, which produce movements of the eyes that compensate for self-motion. When this "vestibulo-ocular reflex" (VOR) works well, images remain stable on the eyes regardless of how fast we're moving. When it fails, both image stability and our overall sense of balance are compromised. In fact, dizziness and other vestibular disorders are one of the most common complaints of elderly patients, yet relatively little is known about the neurobiology of the system.

To perform accurately, the neural circuit for the VOR must solve a simple computational problem: eye movement must be exactly proportional (equal and opposite) to head movement. How do neural circuits instantiate linear signal transformations given that synapses and firing properties of neurons are thought to be inherently nonlinear? What mechanisms are used to ensure accuracy of the behavior, and what goes wrong in patients with vestibular disorders? To address these questions, the du Lac laboratory has been probing the cellular and synaptic physiology of neurons in the central circuit for the VOR in brainstem slices in the context of behavioral analyses of eye movements in mice. Although their visual acuity is poor compared with humans, performance of the VOR is excellent in mice, and the neural circuitry appears to be highly conserved evolutionarily. This has allowed the du Lac lab to exploit the molecular genetic tools developed for mice in conjunction with extensive knowledge about human and nonhuman primate eye movements.

Electrophysiological recordings of the central vestibular system in acute brainstem slices reveal that the intrinsic firing properties of vestibular nucleus neurons are remarkably linear over the entire firing range from zero to several hundred spikes each second. The ability to sustain high firing rates is conferred by high expression of sodium channels with special properties that minimize voltage dependent inactivation and of Kv3 potassium channels, which serve to rapidly repolarize the action potential. Calcium-dependent potassium currents slow depolarization during the interspike interval, thereby extending the input range over which the evoked firing rate is linear. This intrinsic linearity is complemented by exceptional properties of transmission from vestibular nerve synapses, such that the evoked firing rate is proportional to the vestibular nerve firing rate over the entire behaviorally relevant range. Several specializations of the vestibular nerve synapse contribute to rate-invariance, including minimal presynaptic calcium accumulation, multiple presynaptic release sites with low release probability, effective clearance of glutamate by transporters and rapid kinetics of postsynaptic glutamate receptors. Intriguingly, the gain of both intrinsic firing and synaptic transmission can be modified with stimuli that produce specific patterns of postsynaptic hyperpolarization, providing a plausible means by which synaptic inhibition from the cerebellum could calibrate the performance of the VOR.

Peggy Mason, Ph.D.
Professor and Chair,
Committee on Neurobiology
University of Chicago
April 12, 2010

Timing Critical Behaviors with the Reaction to Pain

Like Dr. du Lac's work, the Mason lab at the University of Chicago examines the question of how networks process an ever-changing environment to generate appropriate behavioral responses. Dr. Mason's work looks at how neural circuits adapt to changing environmental conditions; in this case, with a specific emphasis on pain perception (nociception) in various environments. An organism experiencing severe pain must still be able to perform all biological functions critical for survival. As a consequence of this, the experience of pain can change depending on the needs of a given situation. Dr. Mason's lab is working to address exactly how the network properties underlying nociception can be modulated upon encountering different environmental stimuli in order to promote an organism's well-being.

Pain modulatory pathways modify nociceptive transmission so that the same noxious stimulus can be perceived differently by different individuals or by one individual under different circumstances. The pathways responsible for modulating pain perception descend from the brainstem to the spinal cord, with the ultimate result that the synapse between incoming nociceptors (pain sensors) and dorsal horn cells is modulated. The final common pathway for pain modulation arises from neurons in the medullary raphe magnus (RM), which project to the superficial dorsal horn. RM supports both opioid analgesia and hyperalgesia, or increased pain responsiveness that accompanies persistent pain conditions. Two different populations of non-serotonergic RM neurons are thought to exert opposing effects on pain transmission. In the quest to understand the role of these two populations of pain modulatory neurons, the analgesic effects of morphine have provided a useful entry point.

In anesthetized rats, OFF cells tonically increase their activity in response to analgesic doses of opioids and are thought to tonically inhibit nociceptive transmission. ON cells are tonically inhibited by analgesic manipulations and are thought to tonically facilitate nociceptive transmission. The model of tonic ON cell facilitation and tonic OFF cell inhibition of nociceptive transmission to produce tonic states of hyperalgesia and analgesia has never been fully tested in the unanesthetized animal. To fill this gap, Kevin Hellman in the Mason lab examined the effects of morphine on ON and OFF cell activity in the unanesthetized mouse. He recorded both the background activity and the responses to noxious paw heat of RM cells before and after an analgesic dose of morphine. Hellman and colleagues found that under baseline conditions, ON cells burst and OFF cells paused in response to noxious stimulation. The ON cell activity just prior to the peak of the motor withdrawal from noxious heat correlated with the magnitude of the withdrawal. This correlation suggests that ON cells facilitate the magnitude of the motor response to noxious stimulation. To the researchers' surprise, OFF cell activity was significantly greater prior to stimulation trials that resulted in a withdrawal than before trials when no withdrawal occurred. This finding contradicts the predictions of the tonic model described above, which holds that tonic OFF cell activity should produce a state of analgesia and therefore no withdrawal. It therefore appears that a dynamic decrease in OFF cell activity rather than a tonic absence of OFF cell activity serves a pro-nociceptive function. As the timing of the OFF cell pause correlated with the onset of the motor withdrawal from noxious heat, the OFF cell pause appears to mediate an inhibitory rebound of motor withdrawals, which results in synchronizing the withdrawal. These results suggest that nociceptive information ascends from the spinal cord to RM and that the descending output from RM then critically modulates spinal circuitry to sculpt the motor withdrawal.

Armed with an understanding of how ON and OFF cells modulate nocifensive withdrawals under baseline conditions, the lab then recorded ON and OFF cell activity in the unanesthetized mouse during opioid analgesia. In contrast to results in anesthetized rats, there was no change in the tonic activity of ON and OFF cells after morphine administration. However, morphine administration completely suppressed the ON cell burst and the OFF cell pause elicited by noxious stimulation. Moreover, after morphine, ON cell activity was not correlated to withdrawal magnitude and the latency to the OFF cell decrease in activity (the longest interspike interval after stimulus onset) was not correlated to the latency to withdrawal onset. These results demonstrate that RM does not actively produce a state of analgesia. Rather, morphine simply disables the pro-nociceptive contributions of RM to spinal withdrawals. They then found that withdrawals in the presence of morphine were smaller in magnitude and took longer to reach peak magnitude.

Just as opioids disable the facilitating influences of RM on motor withdrawals, there appear to be natural circumstances when the pro-nociceptive influences are preemptively disabled. Madelyn Baez and Hayley Foo in the Mason lab found that OFF cells fire and ON cells are silent during micturition. Accompanying this activity pattern, animals are unresponsive to noxious stimulation for the duration of voiding. Along with this, the lab has identified a similar activity pattern when RM facilitation of withdrawals appears to be disabled, namely during eating. As is the case during micturition, ON cells are silent and OFF cells are excited during eating. Moreover, animals are unresponsive to noxious stimulation during this time, an effect that is mediated by RM. These results suggest that during behaviors such as voiding and eating that are critical to survival, reactions to noxious stimulation are not facilitated as they are under normal, quiet waking conditions. In sum, disabling the normal RM facilitation of spinal nociceptive circuits allows critical behaviors to continue uninterrupted.

Bruce S. McEwen, Ph.D.
Alfred E. Mirsky Professor
Harold and Margaret Milliken Hatch
Laboratory of Neuroendocrinology
The Rockefeller University
May 10, 2010

Sex, Stress and the Brain: Hormone Action above the Hypothalamus via Novel Mechanisms

Just as the most successful social networks are fluid and flexible, so too are the connections that make up the mammalian brain. Like social networks, the neural networks that make up the brain are shaped, for better or worse, by their surroundings. The McEwen Lab looks at the effects of sex, stress and metabolic hormones on shaping neural networks and subsequent behavior. Understanding how the brain remains flexible in order to respond to changing environmental conditions may help to explain how the environment impacts the development of cognitive disorders, as well as mood/anxiety disorders, and cognitive decline later in life.

The McEwen lab studies how stress and sex hormones act on the brain. The adult brain is much more resilient and adaptable than previously believed, and "adaptive structural plasticity" involves growth and shrinkage of dendritic trees, turnover of synapses and limited amounts of neurogenesis (cell birth) in the dentate gyrus of the hippocampal formation. Neural activity resulting from physical activity and experiences, including those that are threatening and stressful, result in structural, as well as neurochemical, changes in the brain. Sex, stress and metabolic hormones play a significant role in many forms of adaptive plasticity.

Stress and sex hormones help to mediate such plasticity, which has been extensively investigated in the hippocampus, as well as, to a lesser extent, in the prefrontal cortex and the amygdala, all of which are brain regions that are involved in cognitive and emotional functions. Stress and sex hormones exert their effects on brain structural remodeling through non-genomic, indirect genomic, and both classical genomic and non-genomic mechanisms, and they do so synergistically with neurotransmitters and other intra- and extracellular mediators. Estrogen, for example, has been shown to play a role in synapse formation in the hippocampus, and in stress-induced remodeling of dendrites and synapses in the hippocampus, amygdala and prefrontal cortex of the brain.

There is a cyclic variation in spine synapse density on CA1 pyramidal neurons during the estrous cycle of female rats that is caused by the increase in estradiol levels during the first phase of the cycle. This increase is then reversed by the progesterone surge at the time of ovulation. A similar cyclicity is seen in mouse and rhesus monkey and in prefrontal cortex, as well as hippocampus, with a recent report also showing such variation of spine synapse density in the primary sensorimotor cortex. Based upon extensive studies in rat and mouse hippocampus, a predominant mechanism for synapse formation, turnover and maturation involves non-genomic actions of estrogen and progestin receptors in dendrites and presynaptic nerve terminals.

As far as stress and stress hormones, the brain is the key organ of the response to stress because it determines what is threatening and, therefore, stressful, as well as the physiological and behavioral responses that can be either protective or damaging. The hippocampus was the first brain region besides hypothalamus to be recognized as a target of glucocorticoids. The amygdala is important in fear and strong emotions, while the prefrontal cortex is involved in attention, executive function and working memory. Hippocampal and medial prefrontal cortical neurons become shorter and less branched, and dentate gyrus neurogenesis is suppressed by repeated stress, whereas amygdala and orbitoprefrontal cortical neurons show signs of hypertrophy after repeated stress. This promotes impairment of hippocampal-dependent memory and enhances fear and aggression, as well as impairing attention set shifting, a form of executive function that indicates cognitive flexibility.

Dr. McEwen ended his talk by addressing the fact that there are several translational studies on the human brain showing that the effects seen in animal models have relevance to normal and abnormal human brain structure and function. Indeed, restrictions of adaptive plasticity, i.e., a loss of resilience, may be a key aspect of mood, anxiety and cognitive disorders as well as age-related cognitive decline.

Michael Greenberg, Ph.D.
Nathan Marsh Pusey Professor of Neurobiology
Head, Department of Neurobiology
Harvard Medical School
Sept. 9, 2009

Signaling Networks that Regulate Synapse Development and Cognitive Function

As the previous talks have demonstrated, proper synapse formation and activity are critical to the production and modification of complex behavior. Dysfunction of the mechanisms guiding these processes can lead to the progression of a variety of cognitive diseases, which is the main area of interest for Michael Greenberg's lab. Using an array of molecular assays in combination with high-throughput sequencing technology, the Greenberg lab attempts to identify specific mechanisms responsible for disruption of synaptic development and signaling in response to environmental stimuli. Here he develops the relevance of his research to human cognitive disorders such as autism and mental retardation.

Our interactions with the outside world trigger changes at neuronal synapses that are critical for brain development, sensory perception and higher cognitive function. The Greenberg lab's research has focused on 1) the identification of a genetic program that is activated by neuronal activity, 2) signal transduction mechanisms that carry the activity-dependent signal from the membrane to the nucleus, and 3) regulators of this experience-dependent process that affect synapse development and plasticity. The lab is particularly interested in activity-dependent processes whose dysfunction can lead to the development of human diseases of cognition such as autism and mental retardation.

Using global screening techniques such as microarray profiling and high-throughput transcriptome sequencing, the Greenberg lab has identified a number of genetic loci whose expression is regulated by membrane depolarization and calcium influx, which in turn control processes such as dendritic arborization, spine development, protein interactions, local control of protein translation at the synapse by micro-RNAs, and the relative number of excitatory and inhibitory synapses. One main focus of the Greenberg lab is to identify the proteins that bind to the promoters of these genes and are responsible for their activity-regulated expression using chromatin immunoprecipitation combined with high throughput sequencing.

One such study has led to a deeper understanding of the mechanisms that regulate the activity-induced transcription of the gene that encodes Brain-Derived Neurotrophic Factor (BDNF), a protein important for proper development of the central nervous system and neuronal plasticity. Control of BDNF expression in the brain is complex—there are seven transcriptional promoters of BDNF in mammals that generate a host of mRNA transcripts, all of which give rise to an identical BDNF protein. Promoter IV is most highly induced by calcium influx in vivo, and is expressed in the mammalian brain. There are several regulators of BDNF promoter IV expression, including CREB, MEF2, USFs, CaRF and MeCP2. Recent data from the Greenberg lab suggest a general model in which experience-dependent stimuli trigger the dynamic modification of transcription factors such as CREB, MEF2 and MeCP2, leading to their altered function in promoting the expression of a genetic program that controls key processes such as synapse development. Another transcription factor, Npas4, is upregulated after neuronal activity and calcium influx, leading to the formation or stabilization of inhibitory synapses onto excitatory neurons. Since many disorders of cognition are correlated with changes in the number of synapses or an imbalance between excitation and inhibition in the nervous system, understanding the complex genetic program that is controlled by these activity-regulated transcription factors may reveal how its dysregulation may lead to neurological diseases.

Rita Balice-Gordon, Ph.D.
Professor
School of Medicine
Department of Neuroscience
University of Pennsylvania
Jan. 25, 2010

Cellular and Synaptic Mechanisms Underlying Autoimmune Anti-Glutamate Receptor Disorders of Memory and Cognition

Dr. Rita Balice-Gordon is also interested in the mechanisms underlying synaptic dysfunction, which often lead to cognitive pathologies. In particular, the Balice-Gordon lab is interested in disorders stemming from glutamate neurotransmission, which has a well-known role in facilitating learning and memory. One such class of disorders is autoimmune in nature, where an organism's own antibodies mistakenly attack its glutamate receptors, leading to severe cognitive difficulties. Dr. Balice-Gordon's lab utilizes two different model organisms, the mouse and the zebrafish, to study this problem from the cellular, electrophysiological and behavioral perspectives, in hopes of producing a broader understanding of this complex type of disorder.

Synaptic plasticity is thought to underlie mechanisms of memory, learning and cognition. Central to these neurological functions is the proper synaptic localization and trafficking of neurotransmitter receptors, including excitatory glutamate NMDARs and AMPARs. The roles of these receptors at the synaptic and cellular level have been established through animal models in which the receptors have been genetically or pharmacologically altered. In humans, the role of these receptors in memory, learning and cognition comes from more indirect approaches such as pharmacological drug trials (e.g., NMDAR antagonists in schizophrenia) and analysis of brain tissue from patients with disorders such as Alzheimer's disease or schizophrenia, in which multiple genetic or molecular pathways are affected.

Dr. Balice-Gordon's presentation focused on two recently discovered human autoimmune disorders of memory, learning and cognition, and psychosis, in which the function of NMDA receptors and AMPA receptors is directly affected by a patient's antibodies. These disorders are naturally occurring models of human memory dysfunction that are characterized by several unique phenomena: they are relatively frequent, cause severe memory loss, can be lethal but are potentially treatable, often affect children, and patients' antibodies bind preferentially to hippocampus, cerebellum and striatum. The presence of highly specific serum and cerebrospinal fluid antibodies to extracellular domains of NMDA receptor and AMPA receptor subunits have been used to develop diagnostic tests. Recently, the Balice-Gordon lab has established that the cellular and synaptic mechanisms underlying these novel and life-threatening anti-glutamate receptor encephalopathies, as well as mechanisms of recovery, provide insights into cellular and circuit dysfunction caused by patients' antibodies. Importantly, they begin to connect synaptic and circuit dysfunction with the behavioral abnormalities that are hallmarks of these disorders.

The M.R. Bauer Distinguished Lecturer Series Summaries 2009–2010

Introduction

Each year the M.R. Bauer Distinguished Lecturer Series brings to campus two eminent investigators in neuroscience. These distinguished scientists spend a full week at the Volen Center, during which time they give one public lecture plus more technical presentations of their work. A key part of the visitors' schedules during their week-long stays are their informal visits to Volen Center labs, where they engage in one-on-one or small group sessions with graduate students and postdoctoral fellows in the labs. These informal exchanges often lead to the development of new ideas and often to the development of future research collaborations.

For the second time in the history of the M.R. Bauer Distinguished Lecturer Series, "one" of our distinguished lecturers was represented by a team; Allison Doupe and Michael Brainard, both from the Keck Center for Integrative Neuroscience at the University of California at San Francisco. The "second" visitor was Professor Larry Zipursky from the Department of Biological Chemistry at the University of California at Los Angeles. Dr. Lorna Role from the State University of New York at Stony Brook, who was unable to make her scheduled visit last year, was happily able to join us for the 2009–2010 series.

Allison Doupe, Ph.D.
Professor of Physiology and Psychology
Keck Center for Integrative Neuroscience
University of California at San Francisco
March 16, 2009

What Songbirds Can Teach Us About Basal Ganglia Circuits, Social Context and Plasticity

Social networks and social communication are not restricted to humans. Other species, such as songbirds, also have developed the ability to communicate vocally. One such species of songbird, the zebra finch, provides an excellent model for studying how social context affects the learning and maintenance of vocal communication. The Doupe lab studies the zebra finch brain circuits responsible for song learning, which occurs in a subset of neurons thought to play a role in enabling lifelong learning. Since song production requires both the capability to learn and produce song, this system provides not only a powerful model for examining not only the plasticity of learning throughout life but also a better understanding of conditions affecting speech production.

The Doupe lab studies the function of basal ganglia circuits in learning and behavior, using the songbird model system. Songbirds provide one of the few animal models for speech learning; like humans, they need to hear the sounds of adults during a sensitive period, as well as the sound of their own voice while learning to vocalize. They also possess networks of brain regions that include a hierarchy of auditory areas, a motor pathway for vocal production and a "cortical"-basal ganglia circuit known as the anterior forebrain pathway (AFP). This cortical network, which has many similarities to regions of the mammalian brain, is required for song learning and has enabled investigation of the neural mechanisms involved in this complex process.

Dr. Doupe's presentation focused primarily on the basal ganglia circuit of the brain for song and its function in sensorimotor learning and production. The first part of her talk discussed the cortical output nucleus of the AFP, called LMAN (lateral magnocellular nucleus of the anterior nidopallium), which projects directly to brain regions controlling motor output. Early studies of LMAN indicated that this system was critical for vocal learning, but not for adult song maintenance. Collaborative work between the Doupe lab and Dr. Michael Brainard's lab, however, has shown that this nucleus is essential throughout life for song plasticity. Dr. Doupe's talk reviewed the neurophysiological and behavioral data that have shed light on how LMAN may function to enable learning. This nucleus appears to provide both stability and variability to the learning process, as its firing rate can either be time-locked with the pattern of a song, or markedly more variable, depending on the social context and stage of learning. Thus, songbird research has suggested that one of the critical functions of basal ganglia circuits, perhaps in all vertebrates (including humans), may be to create behavioral variability. Such variability has long been known to be important for trial-and-error learning, but studies of the songbird AFP suggest a specific neural source for this variation. Moreover, LMAN seems to actively contribute to a switch from a "performance" state, in which the bird sings at its best, stereotyped song version, to a variable, more "exploratory" mode that may be particularly important for learning. In this regard, the AFP also sheds light on a potential locus of action of social signals, which are known to influence learning in many animals, including humans.

The second part of Dr. Doupe's presentation included a step-wise analysis and manipulation of the different nuclei within the circuit of the AFP in order to examine where and how social context-dependent variability might emerge. The data demonstrate that trial-by-trial variability of firing is not a property of cortical inputs to the AFP, but emerges within the AFP network, perhaps within the interactions of striatal and pallidal neurons. This provides yet another clue that variability is important and actively generated by the brain's basal ganglia circuits, and raises hypotheses about neuromodulatory regulation of this process. Finally, inactivation of LMAN's inputs showed that disruptions of the circuit can in some cases increase, rather than decrease, LMAN activity, suggesting mechanisms for the different diseases of basal ganglia. These diseases range from a movement initiation deficit (as in Parkinson's disease) to uncontrollable movements (as in Huntington's disease). Because the songbird AFP is a discrete cortical-basal ganglia circuit specialized for a simple behavior, it is a potentially very powerful model for elucidating the general function of such circuits, both in normal and disordered learning and motor control.

Michael Brainard, Ph.D.
Associate Professor
Keck Center for Integrative Neuroscience
University of California at San Francisco
March 15, 2010

Contributions of Basal Ganglia to Song Learning

The Brainard Lab also investigates the importance of social networks in learning using the zebra finch model system. Brainard's research focuses on the role of auditory feedback in song learning, with the lab working toward uncovering the specific neuronal networks necessary for song learning and production. Elucidating the brain regions responsible for song learning may well have broad implications for our current understanding of how human language is acquired and maintained.

Research in the Brainard lab focuses on the general question of how performance-based feedback is used by the nervous system to learn and maintain complex motor skills. As a specific example of this question, researchers in the lab study how auditory feedback contributes to vocal learning in songbirds. The study of song learning offers the advantages of a well-described behavior that exhibits a variety of general features of learning, while also being subserved by a discrete and extensively investigated set of brain regions. These features make song learning a useful model for studying the mechanisms that contribute to vertebrate sensory and sensorimotor learning in general, as well as specific components of human language learning. Song and speech acquisition exhibit strikingly similar requirements for memorization and vocal practice, during both early development and for maintained auditory feedback throughout life.

The first part of Dr. Brainard's presentation focused on the question of how song behavior in adult birds is shaped by auditory feedback. Adult birdsong is normally a highly stereotyped behavior that varies little from one rendition to the next. As such, this adult song is often described as a post-critical period behavior that is "crystallized" and refractory to the influence of sensory experience. To test the possibility that adult song could be modified by experience, the Brainard lab developed a novel computerized system for precise online monitoring of song, with controlled and reversible manipulation of feedback. This enabled researchers to demonstrate online influences of auditory feedback on song production, which parallel similar influences on human speech. Moreover, by using this system to provide differential feedback to reinforce a subset of naturally occurring vocalizations, they have been able to rapidly drive precise, adaptive changes to adult song. These data showed that large adaptive changes could be directed in post-critical period song. More generally, the results indicate that the small natural variations present in the performance of well rehearsed motor skills are not merely uncontrolled "noise," but rather, provide meaningful "motor-exploration" that can be used by the nervous system in learning.

The second part of Dr. Brainard's presentation described investigations of the role of the brain's basal ganglia circuitry in feedback-dependent learning. There is a striking dissociation between the importance of avian basal ganglia circuitry for production versus plasticity of song. In adult birds, lesions of the output nucleus of this pathway (nucleus LMAN) show little overt effect on the structure of song that the birds produce but prevent plasticity of song in response to perturbations of feedback such as deafness. These data demonstrate that the pre-motor circuitry for generation of learned song does not reside in the basal ganglia, but rather that this circuit plays a crucial role in enabling performance-based feedback to drive changes in song.

The Brainard lab uses neural recordings as well as perturbations of activity in LMAN to investigate how this nucleus contributes to learning. These experiments demonstrate that signals from basal ganglia circuitry contribute to modulation of adult song structure in a manner that is consistent with a role in song learning. The researchers have shown that signals from LMAN have the capacity to direct specific, real-time changes to features of individual syllables (such as pitch or amplitude), which suggests the possibility that LMAN may direct changes to song under conditions of normal learning. Additionally, lesion and inactivation studies have demonstrated that under natural conditions of song production, signals from LMAN actively modulate song variability. Collectively, these experiments suggest that in songbirds, and perhaps more generally, frontal-basal ganglia circuits contribute to motor learning and performance by 1) introducing variability in motor output in the service of 'motor exploration' and 2) biasing motor output toward those behavioral variants that give rise to better outcomes.

Larry Zipursky, Ph.D.
Professor
Department of Biological Chemistry and
Investigator, Howard Hughes Medical Institute
David Geffen School of Medicine
University of California at Los Angeles
November 9, 2009

Dscam Proteins in Neural Circuit Assembly

The third summary we present from the 2009-2010 Distinguished Lecturer series is from Dr. Larry Zipursky, whose lab focuses on the mechanisms behind nervous system development. Specifically, the Zipursky lab studies how developing neurons find the proper targets when extending their axons for the very first time. Building on important studies from the middle of the 20th century, researchers in the Zipursky lab have identified a gene that produces thousands of different isoforms, each of which contribute to give a neuron a particular "identity." This process has been shown to be critical both for target identification during nervous system development and for maintaining cell identity within a neural network. Without these cell identification mechanisms, improper connections would be made throughout the brain, leading potentially to a range of cognitive disorders, including Down syndrome.

An animal's behavior is determined by neural circuits: the pattern of connections between neurons, how neurons communicate with one another and the effect of experience on modifying the structure and function of these circuits. Dr. Zipursky is interested in understanding how neural circuits form during development, which is a problem of daunting complexity. In the human brain, there are roughly 10^{12} neurons, each forming on average about 1,000 connections. In the brain of the fruit fly, *Drosophila melanogaster*, hundreds of thousands of neurons are interlinked by a network of millions of synaptic connections. The developmental strategies by which neural circuits form remains a central question in neurobiology.

Based on a series of experiments carried out between 1940 and 1963, Roger Sperry proposed that the formation of neuronal circuits relies on specific chemical recognition between different neurons. Indeed, he stated that neurons "…must carry some kind of identification tags… by which they are distinguished from one from another almost at the level of single neurons." Nearly a decade ago, researchers in the Zipursky lab discovered a very large family of cell recognition molecules in *Drosophila* encoded by the *Dscam* gene. These researchers speculated that through a process of alternative splicing, these molecules could function as Sperry-like proteins to provide cellular recognition properties, which could underlie connection specificity. A series of genetic and biochemical studies over the past five years have provided insight into how *Dscam* proteins regulate connectivity.

Studies on *Dscam* uncovered the central importance of the ability of neurons to distinguish between self and non-self during the assembly of neural circuits. The *Dscam* gene potentially encodes some 38,016 isoforms. This includes 19,008 extracellular domains tethered to the membrane by one of two alternative transmembrane segments. Each extracellular domain, or isoform, binds to itself but typically not to any other isoform. This recognition process is used in developing neural circuits to promote self-avoidance, which enables the multiple axonal and dendritic branches of a neuron to distinguish between self and non-self. Each neuron expresses a unique combination of isoforms and thus a unique cell surface identity. Self-interactions lead to a contact-dependent repulsive response. This self-avoidance plays a crucial role in promoting segregation of axon branches, as well as allowing highly branched dendrites of one cell to uniformly cover a receptive field, as well as to share the same receptive field with the branches of other neurons. In more recent studies, the Zipursky lab has shown that repulsive interactions between processes of the same cell mediated by different *Dscam* isoforms also plays a crucial role in forming specific patterns of synaptic connections in the fly visual system. *Dscam* proteins must collaborate with many other cell recognition molecules to regulate interactions between processes of the same cell, processes of cells of the same class and interactions between processes of different cell classes.

Lorna W. Role, Ph.D.
Professor and Chair
Department of Neurobiology and Behavior
and Center for Nervous System Disorders
State University of New York, Stony Brook

Neuregulin – Signaling and Nicotinic Receptor Modulation of Cortico-Limbic Circuits

Along with the brain chemical glutamate, cholinergic neurotransmission has been extensively implicated in cognitive dysfunction and disease and is the topic of interest for Dr. Lorna Role. The Role lab studies a particular signaling network that maintains and promotes healthy cholinergic cells in the brain. When these signaling cascades break down, cognitive problems result, often presenting in the form of schizophrenia. Dr. Role's work is a prime example of how very small changes in protein signaling can cause very severe and widespread changes in behavior.

In the words of Dr. Role, "It all started with a molecularly-brave graduate student in the lab seeking to identify the 'factor' that regulated the expression of nicotine-gated channels (or nAChRs). She cloned and identified this molecule from a chick spinal cord library in 1993. In 1998, she published her thesis on the neuronal Acetylcholine Receptor Inducing Activity or 'nARIA' in Neuron. The thesis included the sequence of what turned out to be an enormous gene, comparing it, as is traditional, with its mouse and human relatives, and demonstrating its activity as a regulator of nAChR expression." Little did she or Dr. Role know at the time that nARIA would turn out to be a splice isoform of Neuregulin 1, which has since been identified as a schizophrenia susceptibility gene implicated in cholinergic signaling.

Central cholinergic systems have been strongly implicated in a number of neuropsychiatric diseases including attentional disorders, schizophrenia, depression and Alzheimer's dementia. These cholinergic systems are believed to provide important modulatory control of synaptic excitability. The Role laboratory studies the generation, plasticity and maintenance of cholinergic and cholinoceptive synapses in the mammalian brain. Recent work from this research group has shown that novel classes of signaling molecules, which are products of the *neuregulin-1* gene, are important in the susceptibility to such diseases.

Neuregulin-1-signaling is essential to the maintenance of normal cholinergic circuits, which is accomplished through regulation of the expression of a family of acetycholine receptors *(nAchR)* in the brain. These receptors interact with a number of signaling cascades involved in cell survival, thus keeping cholinergic neurotransmission networks intact. In collaboration with Dr. David Talmage, the Role lab has incorporated behavioral, electrophysiological and genetic techniques to probe changes in cortico-limbic circuitry that result from aberrations in *Neuregulin1* and *nAChR* expression. These studies have led to many striking discoveries and have suggested that many of the cholinergic cells expressing these genes are part of CNS circuits and synapses related to disease, with a particular emphasis on the neuronal circuits underlying the pathological symptoms of schizophrenia.

Volen National Center for Complex Systems Scientific Retreat, 2010

The annual Volen National Center for Complex Systems Scientific Retreat was held on April 6, 2010, at Endicott House, in Dedham, Mass. Endicott House, a former personal estate now owned by MIT, offers a modern meeting facility within a rustic setting located within a 40-minute drive from the Brandeis campus. This year's retreat carried the "networks" theme, with a special focus on disease. It followed our tradition of drawing our speakers from among the Volen Center faculty, along with a guest keynote speaker. The Volen Center speakers, Sacha Nelson, Eve Marder, Nicholas Rohleder, and John Lisman, presented their research relating to a variety of neurologically based diseases. Our guest keynote speaker was Dr. Rosalind Segal from the Dana Farber Cancer Institute in Boston. An important part of our annual retreats is a poster session in which our graduate students have the opportunity to present their ongoing doctoral research to their colleagues. These sessions are always highly interactive and often lead to new collaborations and new ideas.

Tuesday, April 6, 2010

9:00 a.m.
Arrival at Endicott House, Dedham, Mass.

10:00 a.m.
Arthur Wingfield, D.Phil.
Nancy Lurie Marks Professor of Neuroscience and Director, Volen National Center for Complex Systems
Introduction and Welcome

10:05 a.m.
Keynote Speaker:
Rosalind Segal, M.D., Ph.D.
Professor of Neurobiology
Harvard Medical School
Dana Farber Cancer Institute
"Mitogenic Niches in the Brain: Sonic Hedgehog and Proteoglycans"

11:00 a.m.
Sacha Nelson, M.D., Ph.D.
Professor of Biology and Volen National Center for Complex Systems
Brandeis University
"Physiological Genomics in a Mouse Model of Rett Syndrome"

11:45 a.m.
Lunch

12:45 p.m.
Poster Session

1:45 p.m.
Eve Marder, Ph.D.
Victor and Gwendolyn Beinfield Professor of Neuroscience and Volen National Center for Complex Systems
Brandeis University
"Beyond Optimality to the Neuroscience of the Individual Brain"

2:30 p.m.
Nicolas Rohleder, Ph.D.
Assistant Professor of Psychology and
Volen National Center for Complex Systems
Brandeis University
"Stress, Inflammatory Regulation and Disease"

3:15 p.m.
John Lisman, Ph.D.
Professor of Biology and Volen National Center for Complex Systems
Brandeis University
"Understanding Schizophrenia as a Dynamical System: What Happens at the Schizophrenic Break?"

4:00 p.m.
Social Hour and Poster Session

6:00 p.m.
Departure

Rosalind Segal, M.D., Ph.D.
Professor of Neurobiology
Harvard Medical School
Dana Farber Cancer Institute

Mitogenic Niches in the Brain: Sonic Hedgehog and Proteoglycans

Our keynote speaker at this year's retreat, Dr. Rosalind Segal, set the stage by providing insights from her own work on the importance of functional networks as they relate to disease. Her lab at the Dana Farber Cancer Institute examines a prime example of this relationship: how the nervous system develops from neural stem cells and the role of a brain growth factor called "Sonic Hedgehog (Shh)." In her presentation she described how this work has important implications for understanding the effects of disruptions in cellular communication, which are often implicated in the formation of brain tumors.

The Segal laboratory investigates the process of neural development—how the nervous system develops from neural stem cells. Research in the lab focuses on extracellular cues, such as growth factors and morphogens, that direct this complex process. Neural stem cells are self-renewing precursors capable of giving rise to additional stem cells and to differentiated neurons and glial cells. A feature of the specialized niches where stem cells are found in the developing and mature brain is that they contain both critical protein growth factors and specialized proteoglycans. Sonic Hedgehog (Shh) is one such growth factor.

Researchers in the Segal lab are currently studying the mechanisms by which Shh regulates neural stem/precursor proliferation. Using genetic approaches, they have found that Shh interactions with specialized proteoglycans and with the chemokine CXCL12 both promote proliferative responses to Shh. Because mutations that activate the Shh signaling pathway cause brain tumors and other cancers, such interactions are likely to be important in oncogenesis. The Segal lab is currently investigating the ways in which inhibitors of Shh signaling might be used in treating brain tumors that arise from neural precursors, including both medulloblastomas and astrocytomas. Additional studies in the lab have focused on survival pathways in developing neurons. Work from this lab has identified components of a signaling cascade involved in expression of bcl2l2 and in neuronal survival. These anti-apoptotic mechanisms are likely to play a role in the aggressive behavior of brain tumors.

Sacha Nelson, M.D., Ph.D.
Professor of Biology and
Volen National Center for
Complex Systems
Brandeis University

Physiological Genomics in a Mouse Model of Rett Syndrome

Similar to the Segal lab, the Nelson lab focuses on the effects of aberrant signaling between cells. In particular, the lab is interested in understanding how the balance of excitatory and inhibitory inputs into a network can change the resulting behavior of an organism. The Nelson lab is especially interested in understanding Rett Syndrome, where the imbalance of cellular signals can lead to developmental and cognitive impairment.

Rett syndrome is a devastating developmental disorder characterized by a period of normal development followed, after six to eighteen months, by a period of regression. During this period of regression, patients typically lose many of the linguistic, motor and cognitive abilities they had developed before stabilizing. Patients can grow to adulthood but are often severely mentally retarded, unable to converse and have limited use of their hands and legs. Rett Syndrome is an autism-spectrum disorder, but unlike autism, it is due in most cases to a single, X-linked gene. This gene, *Mecp2* (Methyl CpG binding protein 2), codes for a DNA binding protein that recognizes methylated DNA. How disruption of this interaction leads to the disorder is not well understood.

The Nelson lab works with a mouse model of Rett Syndrome in which the *Mecp2* gene has been deleted. Loss of *Mecp2* function produces a shift in the balance between cortical excitation and inhibition in favor of inhibition. This is due to a loss of recurrent excitatory connections between pyramidal neurons. The loss of excitation reduces cortical activity and makes it more difficult to induce synaptic plasticity. At a molecular level, loss of *Mecp2* leads to changes in gene expression that are widespread but vary in different cell types. One category of genes, cell adhesion molecules, is overrepresented in each of the cell types tested. Cell adhesion genes are known to be important for establishing and maintaining appropriate synaptic connections within the nervous system. Dr. Nelson ended his presentation by speculating that *Mecp2* normally orchestrates a cell-type specific transcriptional program of cell adhesion molecules that fine-tunes synaptic strength during the later phases of activity-dependent development.

Eve Marder, Ph.D.
Victor and Gwendolyn Beinfield
Professor of Neuroscience and
Volen National Center for
Complex Systems
Brandeis University

Beyond Optimality to the Neuroscience of the Individual Brain

When searching for potential treatments and therapeutics for disease, one must first consider how a network is constructed and how the given network properties can be modified. Work from the Marder lab suggests that there is no one "blueprint" for building a circuit; rather, there are different network parameters that can all generate a similar end result. Understanding how different types of communication can yield similar responses, and ultimately similar behaviors, has important implications for future drug research.

We all know that no two people are the same, and many assume that all individual humans and other animals will have significant differences in their brains. Nonetheless, it is common for experimentalists to make the underlying assumption that individuals of the same species have essentially identical brains, and so they can repeat experiments on multiple animals to assure the validity of their findings. While replication is essential for all scientific findings, mean data can sometimes be misleading and can hide important truths found in the variability of measurements made from individuals.

Computational work from the Marder lab has demonstrated that similar circuit outputs can be produced with highly variable circuit parameters. This work argues that the nervous system of each healthy individual has found a set of different solutions that give "good enough" circuit performance. Using the crustacean stomatogastric nervous system, researchers in the Marder lab have shown that synaptic and intrinsic currents can vary far more than the output of the circuit in which they are found. These data have significant implications for the mechanisms that maintain stable function over an animal's lifetime, and for the kinds of changes that allow the nervous system to recover function after injury.

This work raises the question of the extent to which neuromodulation can be constant with underlying circuit parameter variation. To address this question, the lab constructed two cell reciprocally inhibitory circuits using the dynamic clamp from biological GM neurons of the crab stomatogastric ganglion. The output of the circuits are described manually while sweeping through a range of synaptic and intrinsic conductances, first in control saline and then in the presence of serotonin. They found that serotonin extends the ranges of parameters that produce alternating bursting. Moreover, although serotonin's effects are highly robust and significant on the entire population, individual networks respond anomalously. These data demonstrate that while neuromodulation may have robust actions on a population, not all individuals may respond as do the majority. These findings have important implications for evolution, as well as some of the challenges that lie in treating all neurological conditions of a similar nature as "the same."

Nicolas Rohleder, Ph.D.
Assistant Professor of Psychology and
Volen National Center for Complex
Systems
Brandeis University

Stress, Inflammatory Regulation and Disease

One possible benefit of not having a single "blueprint" for every circuit is the potential for flexibility in how an organism deals with the ever-changing environment. Stress has long been thought to exacerbate disease, although much of this relationship has remained uncharacterized. The Rohleder lab is seeking to identify specific mechanisms that connect stress with disease.

Stress is continuously discussed as an antecedent of medical and psychiatric disease. Although there is epidemiological evidence for stress being prospectively associated with, for example, cardiovascular disease and depression, much less is known about the specific pathophysiological mechanisms mediating these relationships. Several pathways between the Central Nervous System (CNS) and the periphery are most likely involved. The CNS communicates stress to the periphery mainly through the sympathetic nervous system (SNS) and through the hypothalamus-pituitary-adrenal (HPA) axis. These systems in turn secrete messenger molecules, such as the neurotransmitter noradrenaline, and the hormone cortisol, to further affect a large array of target organs throughout the organism. Changes in the function of these communication systems and peripheral concentrations of their respective mediators in response to acute and chronic stress have been known for several decades. Although the effects on target organs are well-described, it remains unclear exactly how changes in noradrenaline and cortisol induce long-term damage in the organism.

One candidate mechanism is inflammation. Although part of the defense mechanisms against invading pathogens, inflammation is a double-edged sword that can do significant harm in the organism if not properly controlled. Inflammation is the central mechanism leading to atherosclerosis and cardiovascular disease, and is further involved in the development of type 2 diabetes, cancer and inflammatory diseases of the CNS. Important regulators of inflammation are the stress systems described above, i.e. the SNS and the HPA axis. A major research effort in the Rohleder laboratory is to understand the conditions under which stress systems become less effective in controlling inflammation, thus unleashing the destructive potential of inflammatory effector mechanisms, permitting accumulation of damage in the body.

To understand these mechanisms, researchers in the Rohleder lab investigate the effects of acute laboratory and long-term naturalistic stress in humans using a multi-level, multi-system approach. A recent study from the lab followed up on family members of brain cancer patients for about a year, where researchers repeatedly measured the functioning of stress systems and the control of inflammatory mechanisms. Results showed that an intense life stressor alters baseline activity of stress systems, as well as functioning of target systems in a dynamic fashion. Intra-cellular expression of anti-inflammatory transcription factors, for example, decreased over time under stress, and these combined changes permitted peripheral inflammation to increase to levels that signify increased risk for cardiovascular disease. In further studies, the lab is currently investigating whether the way we typically respond to repeated acute stress is predictive of long-term disease development and how this contributes to long-term changes that are part of the aging process.

John Lisman, Ph.D.
Professor of Biology and
Volen National Center for
Complex Systems
Brandeis University

Understanding Schizophrenia as a Dynamical System: What Happens at the Schizophrenic Break?

While many of the previous talks focused on how network disruptions or network malformations can lead to a variety of disease-states, Dr. Lisman's presentation explored how even a healthy network can produce aberrant signals. In particular, the Lisman lab studies how positive reinforcement within a structurally sound network can lead to overstimulation of specific groups of cells, resulting in psychosis.

Schizophrenia affects a significant number of individuals in our society, but the cellular and molecular basis of the disease remains unclear. One important hint comes from the fact that antagonists of the NMDA-type of glutamate receptor can induce many of the positive and negative symptoms of the disease. There has therefore been considerable effort to determine how such antagonists produce disturbances of neuronal function. Indeed, it is not at all clear why an antagonist of a neurotransmitter that is excitatory should produce (rather than quiet) mental activity.

There have been previous indications that NMDA antagonists can strongly affect the thalamus. For this reason, the Lisman lab investigated this at the cellular level, particularly in the nucleus reticularis, which is a group of inhibitory neurons that surround the thalamus. Researchers in the lab have found that an NMDA antagonist produces bursting of these inhibitory cells, and have determined the underlying mechanisms: an unusual type of NMDA receptor (NR2C) affects resting potential, and block of these channels hyperpolarizes these cells, de-inactivating T-type Ca channels, which then produce the observed bursting. Dopamine has been shown to enhance this bursting.

Together with other results in the literature, these findings suggest the first model that explains the sudden onset of the disease, often during stress in late adolescence. The evidence points to a dynamical system with the potential for positive feedback. This system involves the thalamus (notably the nucleus reuniens), the excitation of the hippocampus by this nucleus and the resulting hippocampal-dependent excitation of the dopaminergic cells of the VTA. The release of dopamine closes the loop by promoting bursting of the thalamus. Dr. Lisman suggested that various genetic mutations or developmental problems can push this system closer to the threshold for bursting, creating a predisposition for schizophrenia. Stress, which leads to additional dopamine release, can push the system into a persistent bursting mode maintained by positive feedback, thereby resulting in a psychotic state.

Acknowledgments

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

We also thank two outstanding graduate students in the life sciences at Brandeis, Sara Wasserman and Justin Slawson, for their editorial contributions in the preparation of this annual report.

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

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