Brandeis University

Benjamin and Mae Volen National Center for Complex Systems

August 2014

The M.R. Bauer Foundation Colloquium Series, Annual Scientific Retreat, Distinguished Guest Lecturer Series and Summer Science Research Fellowship

The M.R. Bauer Foundation Colloquium Series, Annual Scientific Retreat, Distinguished Guest Lecturer Series and Summer Science Research Fellowship 2013-2014 Summary

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The 2013-2014 M.R. Bauer Foundation Colloquium Series, Annual Scientific Retreat, Distinguished Guest Lecturer Series and Summer Science Research Fellowship

Introduction

Newspaper headlines remind me of the centrality of our field. News stories both amaze and disappoint, but I cannot help but tie them to neuroscience: new advances in brain imaging technology; rising levels of sleep deprivation in our fast-paced society; creative expression in unlikely venues; appreciations of the sensory qualities of food, nature and love; examples of social behavior, including, regrettably, the violence we read about all too often; progress in research on physical and emotional disabilities and disorders that afflict millions—all of these prove that our field is indispensable for gaining insight and understanding of the human condition.

We are fortunate, then, to have the M.R. Bauer Foundation Colloquium and Guest Lecture Series. This venue gives us an opportunity to explore each other's research and to examine the constantly evolving state of neuroscience. For 20 years, the M.R. Bauer Foundation has emboldened us to study, inquire, and challenge—to conduct leading-edge science. We are being championed in this pursuit.

These talks help ensure that this work is accessible and relatable. Our discoveries, and the possibilities of breakthroughs, give hope to so many. Veterans, parents, the elderly, disabled young people, suffering adults—these are our constituents, and they are vested in our efforts. We reassure them that progress is happening by promoting this work widely and reinforcing its relevance to society.

The Volen Center is proud to host these talks. Every year, M.R. Bauer Foundation-sponsored events enable us to forge camaraderie and reflect on both what is so powerful about our home campus and why neuroscience is so vital. When we return to our labs and engage with our colleagues, including those in the humanities and the social sciences, and most importantly, mentor young scientists, these talks provide inspiration. Together we are illuminating the world through neuroscience.

Leslie Griffith, MD, PhD
Nancy Lurie Marks Professor of Neuroscience
Director, Volen National Center for Complex Systems

The M.R. Bauer Colloquium Series Summaries

Introduction

Isaac Asimov (1920-1992) once said, “The human brain, then, is the most complicated organization of matter that we know.” Billions of neurons communicating in organized networks give rise to our experience of sensory input and our overall perception of the world. This communication goes entirely unnoticed unless there is a glitch – a misfire that throws off the delicate balance between excitation and inhibition that forms the highway of communication within the brain.

The brain is plastic, constantly changing with learning and experience. These changes take place particularly at the level of the synapse and dendrite spine, the areas of the neuron that send and receive messages. Synaptic transmission is a vital process in normal brain functioning, and is a process that can change with learning. For example, as the work of one speaker shows, dendritic spines in the mouse brain have been found to grow or retract depending on experience. Malfunctions in synaptic transmission and neuronal communication have been associated with disorders such as epilepsy and autism spectrum disorder, as illustrated by two of the speakers.

The 2013-2014 M.R. Bauer Colloquium Series explored new developments in the understanding of the functioning of the dendrite and synapse and the role they play in the stability of brain function. Seven distinguished scientists, using model organisms including worms, zebrafish and mice, offered insights into synaptic transmission in the wake of learning and experience. Each speaker has presented a summary of his or her work, which is preceded by a brief introduction set in italics that explains the presentation in a more general framework of synaptic transmission in the face of a plastic, changing brain.

Joshua Kaplan, PhD
Department of Molecular Biology and Harvard Neurobiology Department
Harvard University
(September 11, 2013)

From compost to the clinic: using *C. elegans* to study psychiatric disorders

While much about the autism spectrum disorder is still unknown, it is thought to be a disorder of communication between neurons. Small changes in the construction of a synapse, the spot where one neuron communicates with another, can lead to altered transmission of messages. Understanding how transmission is altered could suggest new treatments for this disorder. In his colloquium, Dr. Kaplan discussed his research exploring how genetic mutations can lead to altered synapse formation and transmission.

It is estimated that 1 in 68 children have an autism spectrum disorder. The cause of autism is not yet understood, and it is unlikely that there is one causal factor that can be linked to each disorder that falls within the autism spectrum. In fact, current studies suggest that mutations in approximately 500 genes are linked to autism spectrum disorder. Although many of these genes encode proteins that are localized at synapses, the sites of connection and communication between neurons, relatively little is known about how these mutations alter synaptic transmission.

The Kaplan lab uses a simple model organism (the worm *Caenorhabditis elegans*) as a genetic platform to investigate the impact of candidate genes on synaptic transmission, brain development and behavior. They have found that three genes linked to autism (NRXN, NLGN and MEF2) regulate the kinetics of neurotransmitter release, and therefore neurotransmission, at synapses in *C. elegans*. In addition, they found that mutations in mouse NRXN also alter the kinetics of neurotransmitter release.

On the basis of these findings, the Kaplan lab proposes that changes in release kinetics may play an important role in the cognitive and developmental features of autism spectrum disorder. They plan in the future to use *C. elegans* as a model to determine how other autism candidate genes alter brain signaling, and to test the idea that altered neurotransmitter release kinetics is a common cellular defect in different forms of the disorder.

Michael Young, PhD
Laboratory of Genetics
The Rockefeller University
(September 18, 2013)

Genes controlling sleep and circadian rhythms

The circadian clock regulates rhythms of the body, such as the sleep/wake cycle. The process of sleep is regulated by the activity of many proteins, and mutations in the genes that code for these proteins can lead to altered sleep cycles. For example, a mutation seen in the fruit fly Drosophila*, called insomniac, reduces the duration and amount of sleep. There are, however, many other proteins involved in the sleep/wake cycle, and the genetics behind these proteins and processes are still being identified. In his colloquium, Dr. Young discussed his work exploring the genetics and molecular mechanisms of sleep.*

Studies of the molecular basis for circadian (24-hour) rhythmicity began in the early 1980s with a focus on the fruit fly *Drosophila*. This work revealed that circadian clocks are formed through the actions of a small group of genes that are largely conserved in the animal kingdom. Interactions among these genes and their proteins produce circadian molecular oscillations at the level of individual cells. These molecular clocks are active in most animal tissues and establish overt rhythms in physiology and behavior.

A prominent behavior regulated by the circadian clock is sleep. However, sleep is also regulated by homeostatic controls that members of the Young lab are attempting to define genetically. In a forward genetic screen in *Drosophila*, they recognized a mutant with severely reduced sleep. The mutation, *insomniac*, affects both the consolidation and the duration of sleep. The insomniac protein is a member of the BTB/POZ superfamily, which includes many proteins that function as adaptors for the Cullin-3 (Cul3) ubiquitin ligase complex. Insomniac can physically associate with Cul3, and the Young lab found that that reduction of Cul3 activity in neurons recapitulates the insomniac phenotype. The extensive evolutionary conservation of insomniac and Cul3 suggests that protein degradation pathways may have a general role in governing the sleep and wakefulness of animals.

An RNAi-based screen for genes affecting sleep duration in *Drosophila* indicated that two genes essential for normal cell cycle progression, Cyclin A (CycA) and Regulator of Cyclin A 1 (Rca1), also function in post-mitotic neurons to promote sleep. CycA is expressed in approximately 40 to 50 neurons in the fly brain, and most CycA+ neurons are arranged in cell clusters that are intermingled with neurons known to regulate circadian behavioral rhythms. Cyc A+ neurons express the receptor for PDF, a neuropeptide released by pacemaker cells with a circadian rhythm, suggesting that Cyc A+ cells monitor circadian pacemaker activities while promoting the homeostatic control of sleep. Genetically programmed changes in the electrical activity of some CycA-expressing cells substantially alter patterns of sleep.

Elly Nedivi, PhD
Department of Brain and Cognitive Sciences
Massachusetts Institute of Technology
(January 29, 2014)

In vivo imaging of coordinated excitatory and inhibitory synaptic dynamics on pyramidal cell dendrites.

Is it possible for an old dog to learn new tricks? How does the adult brain change as learning occurs? Early research suggested that the adult brain was hardwired and unable to create new neurons or remodel existing connections. However, the connections between neurons, the synapses, can be remodeled and reweighted, meaning some connections grow stronger, while some grow weaker. In her colloquium, Dr. Nedivi discussed her work examining how adult changes in synapse connectivity can change brain function.

While it may be thought that the excitation of neurons — the activation of neurons and the sending of messages from one neuron to the next — is most important in cognition, the flip side — the inhibition of neurons — is also vitally important. The role of inhibition within cortical circuits has recently gained prominence, as it has become clear that the balance of excitation/inhibition is critical to proper brain development as well as for cognitive function. Indeed, many mental and neuropsychiatric diseases have been linked to deficits in inhibitory function. Yet our understanding of how inhibitory connectivity is modified by experience and how that relates to the excitatory network is minimal. In this colloquium, Dr. Nedivi discussed her work examining the creation and elimination dynamics of excitatory and inhibitory synapses.

Recent *in vivo* imaging studies demonstrated that changes in sensory experience can drive structural remodeling of inhibitory interneurons in a cell type- and circuit-specific manner. The Nedivi lab recently found that inhibitory synapse formation and elimination occurs with a great deal of spatial and temporal precision, and is often locally coordinated with excitatory synaptic changes on the same dendrite, largely clustered within 10 micrometers. Yet, the hierarchical relationship of clustered inhibitory and excitatory synaptic dynamics remains unresolved in terms of whether the two events occur simultaneously or if one of the two events drives the change, while the other follows it. Does the presence of a dynamic inhibitory synapse destabilize neighboring spines, or do excitatory synaptic changes drive inhibitory synapse dynamics? Are the valence changes coordinated, or are they compensatory? In other words, does excitatory synapse loss drive formation or loss of an inhibitory synapse?

To probe the nature of this "coordination" between inhibitory and excitatory synapse dynamics, the Nedivi lab triple-labeled L2/3 pyramidal neurons in the mouse visual cortex via *in utero* electroporation using yellow fluorescent protein as a cell fill, postsynaptic density-95-mCherry as a postsynaptic excitatory synapse marker, and Teal-Gephyrin as a postsynaptic inhibitory synapse marker. These mice were implanted with cranial windows as adults, and labeled neurons in the binocular visual cortex were imaged *in vivo* at short intervals using spectrally resolved two-photon microscopy. Surprisingly, they observed increased dynamics when imaging at shorter intervals as compared to previous four-day imaging intervals. In her colloquium, Dr. Nedivi explored the kinetics, distribution and probabilities of these dynamic events.

Suzanne Paradis, PhD
Department of Biology
Brandeis University
(March 19, 2014)

Signaling pathways that instruct rapid changes in neuronal connectivity

Communication between neurons is dependent on wiring up synapses, the connections that form the point where a message is sent from one neuron to the next. Experience determines how synapses form. For example, a child born deaf in one ear will not form the number of synaptic connections in auditory cortex that a child with normal hearing would. An understanding of the process behind synapse formation involves understanding the molecular and genetic pathways underlying their development. In her colloquium, Dr. Paradis discussed her work examining the molecular basis of synapse formation.

Most neurons are highly polarized cells containing both an axon through which they convey information by making synaptic connections onto other neurons, and a dendritic arbor through which they receive information via synaptic inputs from other neurons. Each type of neuron in the mammalian central nervous system has a distinctive dendritic arbor, which is typically extensively branched, and this arbor influences the specific function of the neuron in part by ensuring that the proper synaptic connections are made between neurons. Synapses are specialized sites of cell-to-cell contact that mediate communication between neurons in the nervous system and form the basis for all brain functions and human cognition. There are two main types of synaptic connections in the mammalian brain: excitatory glutamatergic synapses and inhibitory GABAergic synapses. The balance between excitatory and inhibitory inputs a neuron receives regulates the overall activity of neuronal networks; disruptions to this balance are the underlying cause of neurological disorders such as epilepsy.

One potential therapeutic treatment for epilepsy would be to restore the normal excitation-inhibition balance in network activity by increasing the number of GABAergic synapses. The work of Dr. Paradis and her group on synapse formation revealed that treatment of cultured neurons with the extracellular domain of the protein Sema4D causes a rapid increase (within two hours) in the density of functional GABAergic synapses. Using an organotypic hippocampal slice culture as an *in vitro* model of epileptiform activity, they demonstrated that acute Sema4D treatment rapidly and dramatically alters the hyperexcitability found in these slices in a manner consistent with a Sema4D-mediated increase in network inhibition. Their studies suggest the tantalizing possibility that Sema4D, as well as other molecules that instruct formation of GABAergic synapses, could be used as a disease-modifying treatment for epilepsy.

In addition, the nervous system has the amazing capacity to transform sensory experience from the environment into changes in neuronal activity that, in turn, cause long-lasting alterations in synaptic connections and dendritic arborization. Surprisingly little is known about the molecular mechanisms by which changes in neuronal activity are translated into changes in neuronal architecture. Dr. Paradis and colleagues recently discovered that the activity-dependent expression of the GTPase Rem2 functions as a critical regulator of activity-dependent dendritic branching, as dialing Rem2 expression up or down in the context of increased sensory experience in an intact circuit decreases or increases dendritic branching accordingly. Overall, their findings suggest that Rem2 is a key molecule linking sensory experience to underlying changes in synapse and dendrite development.

The M.R. Bauer Distinguished Lecturer Series Summaries

Introduction

Every year the M.R. Bauer Distinguished Lecturer program brings to campus two distinguished visitors who spend a full week at Brandeis. These visitors present talks to small and large groups, visit center laboratories, and engage students, postdoctoral fellows and faculty in informational and highly interactive conversations about shared areas of research interests. This year our distinguished lecturers were Arthur Konnerth from the Technical University of Munich and William Harris from the University of Cambridge.

Arthur Konnerth, PhD
Institute of Neuroscience and Neuronal Cell Biology
Technical University of Munich
(November 6, 2013)

The first weeklong visitor, Dr. Arthur Konnerth, uses the mouse as a model system to describe the basic processes behind brain function. During his visit, Dr. Konnerth described his work exploring the stimulus preferences of individual dendritic spines, the area of a neuron where signals are received from other neurons. By employing a new imaging technique his lab pioneered, they have been able to show that stimulus feature preference occurs at the level of the individual dendritic spine, rather than at the level of the neuron.

How do neurons integrate as a system to form representations of sensory stimuli? Neurons in sensory cortices are stimulated by specific stimulus features, such as orientation or motion. However, a single neuron can receive thousands of inputs onto its dendrites, via its thousands of individual dendritic spines. Whether the stimulus preference is the same for each spine located on a single dendrite has been unclear, as studying spine activity had not previously been possible *in vivo*. Here, Dr. Konnerth reports on a novel imaging technique using both patch clamp electrophysiology and microscopic imaging to record the calcium signaling that corresponds to specific dendritic spine activation.

Combining the use of a calcium dye and a low-power, rapid frame rate microscopic recording, individual dendritic spines can be recorded for long periods of time. With this technique, Dr. Konnerth and colleagues have found that dendritic spines that prefer one stimulus are interspersed and distributed through the dendritic arbor of a neuron, and are not clustered together in one area as was previously thought. Thus, the firing patterns that occur for a preferred stimulus feature are computed through the integration of spatially distributed inputs, which code for multiple stimulus features.

William Harris, PhD
Department of Physiology, Development and Neuroscience
University of Cambridge
(April 9, 2014)

There are many, many different types of neurons within the nervous system. In the retina alone there are rods, cones, horizontal cells, amacrine cells and bipolar cells. With so many essential cell types, how is it possible that the correct number of each form during development? The second weeklong visitor, Dr. William Harris, described his work examining the development of retinal cells in the zebrafish as a model for understanding the more general mechanism of neuron formation in all species.

The retina is an accessible part of the central nervous system. Therefore, it is often used to gain insight into the deeper, more complex and less accessible parts of the brain. Indeed, our understanding of other areas of the brain, such as the cerebral cortex, is in part based on biological mechanisms that were first discovered to be essential for the formation and function of the retina. In his colloquium, Dr. Harris addressed the questions of how the retina grows to the correct size and cell number, and how the various neuronal cell types of the retina arise in their correct proportions.

It has been known for many years that retinal progenitor cells are pluripotent, giving rise to different types of neurons. This knowledge comes from clonal analysis, in which single retinal progenitor cells are labeled in such a way that all daughter cells inherit the label. Early clonal analysis in the retina and cerebral cortex showed that such clones varied widely in terms of cell number and cell fate composition. Using four-dimension microscopy, the genesis of such clones can be catalogued *in vivo* in quantitative detail. With this technique, Dr. Harris demonstrated through a statistical analysis of such clones in the zebrafish retina that the simplest explanation for the variability in cell numbers among clones is that there is an intrinsic stochastic machine operating within a set of equipotent retinal progenitors, which causes a probabilistic distribution of cell division modes. A progenitor may, for example, divide to produce two more progenitors, or it may divide to produce two differentiated neurons, or it may divide to produce one progenitor and one differentiated neuron. It is not at present possible to know which of these events will occur before the division, and it may never be possible. But by assigning probabilities to each of these modes of division, one can generate an excellent fit for the experimental distribution of clone sizes actually seen, and therefore for the final size of the retina.

Dr. Harris and his colleagues have recently shown that the distribution of cell fates within clones is also likely to be at the mercy of a stochastic process, one that appears to randomly assign one cell fate or another, as though flipping a coin, with a probability distribution such that all cell types would be generated with appropriate ratios. They have also provided compelling evidence that the stochastic machines that affect cell proliferation and cell fate seem to operate independently of each other. Despite the fact that individual retinal progenitor cells give rise to clones that are highly variable, the total number of differentiated retinal cells and the relative proportions of cell types generated from a given number of equipotent progenitors is basically invariant from one fish retina to the next. Whether similar mechanisms are used to generate other parts of the brain remains to be explored.

Volen National Center for Complex Systems Scientific Retreat 2013

Introduction

The Volen National Center for Complex Systems held its annual scientific retreat on October 18-19, 2013. The work of the keynote speaker, Hod Lipson of Cornell University, set the tone for the theme of the retreat: "Complex Behavioral Systems: *in silico* and *in vivo* Dynamics." Unlike the 2012 retreat, which was held on the Brandeis campus, this year the faculty, postdoctoral fellows and students traveled to the Provincetown Inn, in Provincetown, Mass. Being away from campus allows students and faculty to interact away from familiar surroundings and normal activities, fostering communication and collaboration that many not have occurred in the bustle of normal daily campus life.

In addition to the keynote speaker, four of our Brandeis postdoctoral fellows from the psychology and neuroscience programs discussed their research. As the summaries that follow will make clear, the 2013 retreat offered a glimpse into fascinating research exploring complex systems from the human to the fruit fly, and at all levels in between.

The 2013 Volen Center for Complex Systems Retreat Schedule

October 18, 2013

4:30 p.m.
Poster session and refreshments

6:00 p.m.
Dinner

7:15 p.m.
Keynote speaker: Hod Lipson, Cornell University
"Automating scientific discovery: distilling natural laws from experimental data, from particle physics to computational biology"

8:30 p.m.
Social mixer

October 19, 2013

9:00 a.m.
Lina Ni, Garrity Lab
"A gustatory receptor paralogue controls rapid warmth avoidance in *Drosophila*"

9:45 a.m.
Jonathan Jackson, Gutchess Lab
"The power of memory and attention in aging and Alzheimer's disease"

10:30 a.m.
Coffee break

11:00 a.m.
Tim O'Leary, Marder Lab
"The wisdom of single neurons"

11:45 a.m.
Keith Hengen, Turrigiano Lab
"Firing rate homeostasis in cortical networks"

12:30 p.m.
Lunch

2:00 p.m.
Departure

Hod Lipson, PhD
Creative Machines Laboratory
Cornell University

Automating scientific discovery: distilling natural laws from experimental data, from particle physics to computational biology

Robots have become a normal part of everyday existence, particularly in fields such as manufacturing. One thing that separates the robots of today, however, from the robots of science fiction is adaptability. While robots are faster than humans at the tasks they are designed to carry out, they are unable to adapt their thought processes to deal with unexpected events. This type of versatility would depend on a neural network, or simulated brain, capable of changing or adapting itself — in essence, learning — as the situation arose. In his colloquium, Dr. Lipson described his work creating robots that can learn and adapt to new situations.

Can machines discover scientific laws automatically? For centuries, scientists have attempted to identify and document analytical laws that underlie physical phenomena in nature. Despite the prevalence of computing power, the process of finding natural laws and their corresponding equations has resisted automation. Dr. Lipson's colloquium outlined a series of recent research projects, starting with self-reflecting robotic systems, and ending with machines that can formulate hypotheses, design experiments and interpret the results, to discover new scientific laws. However, as Dr. Lipson explained, while the computer can discover new laws, it is not clear whether we will understand them.

Our ability to have insight into science may not keep pace with the rate and complexity of automatically generated discoveries. Are we entering a post-singularity scientific age, where computers not only discover new science, but now also need to find ways to explain it in a way that humans can understand? Dr. Lipson offered examples from psychology to cosmology, from classical physics to modern physics, from big science to small science, in order to bring some clarity to these issues.

Jonathan Jackson, PhD
Department of Psychology
Brandeis University

The power of memory and attention in aging and Alzheimer's disease

Alzheimer's disease is a leading cause of dementia, a condition that will become more prevalent as the average lifespan increases. The cognitive difficulties, memory lapses and behavioral changes associated with Alzheimer's dementia are due to the build-up of plaques of amyloid, a type of abnormal protein structure. These plaques begin to form roughly 10-15 years before there are obvious symptoms. Therefore, it is imperative to find ways of identifying patients in the beginning stages of this disease. Dr. Jackson discussed his work measuring attentional control as a method of recognizing Alzheimer's disease in the early stages.

Attentional control refers to our ability to maintain and execute internal goals. This control has been shown to be altered as we age. Therefore, measuring attentional control factors such as reaction time and mind wandering can give us important information about human aging.

Subtle changes in participants' reaction time are one attentional control measure that is sensitive to aging and Alzheimer disease (AD). Dr. Jackson discussed his work investigating reaction time models and integrity of white matter in brain regions known to be compromised in AD. White matter is important in the study of neurodegeneration because it is made up of fibers that connect neuronal cell bodies, or the gray matter, in the brain. Decreased white matter volume may indicate that different regions of the brain are less able to communicate with one another. Dr. Jackson and colleagues found that subjects' slowest trials, as well as their overall variability in responding to three tasks of attentional control, were associated with compromised white matter volume. Importantly, they also found hints that this relationship may be stronger in individuals with AD relative to healthy older adults, which suggests that AD patients may suffer from less-efficient connectivity in the brain.

Dr. Jackson also discussed the relationship between the cerebrospinal fluid (CSF) levels of the Aβ42 peptide (a biomarker known to be associated with AD) and errors in attentional control. He found that errors on the Stroop test were associated with AD biomarkers and genetic markers in a sample of healthy older adults. Similar associations were also found using a third measure of attentional control called mind wandering, which occurs when someone abandons the task at hand in favor of thinking about internal, self-focused thoughts. Taken together, these data demonstrate that there are behavioral consequences of AD years before a formal diagnosis. Measures of attentional control converge in such a way that suggest that this ability is uniquely sensitive to changes in healthy and pathological aging.

Tim O'Leary, PhD
Department of Biology
Brandeis University

The wisdom of single neurons

The activity of a neuron is driven by the inward and outward flow of ions, such as sodium, potassium and calcium, which alters the conductance of the cell, making it more or less likely to fire. The careful balance of these ions determines whether a neuron will send a signal to the next neuron, or whether it will be inhibited from sending that message. How do these neurons, and the networks they form through their connections with one another, consistently regulate these conductance changes in order to function properly? In his colloquium, Dr. O'Leary discussed his work examining the cell's ability to balance its physiological processes, a process known as homeostasis. His models encompass both the activity of the neuron itself and its role within a larger network.

The cells that make up our brains — neurons — are diverse and variable in their biophysical and biochemical properties. On top of this, the biomolecules that form the building blocks of all cells (proteins, lipids, ribonucleic acids and so on) are continually being manufactured and degraded. How does our brain maintain function over time in spite of the variability and ongoing turnover of all its components? In his colloquium, Dr. O'Leary summarized work covering two decades that has attempted to answer this question using computational models based on experimental data from crustacean nervous systems. He also introduced some recent work that shows how feedback control (a.k.a. "homeostasis") reconciles variability with consistent, fault-tolerant behavior in single neurons and small circuits and may explain features of experimental data such as correlations in ion channel expression in single neurons.

Keith Hengen, PhD
Department of Biology
Brandeis University

Firing rate homeostasis in cortical networks

Homeostasis is a fascinating property of neuronal networks: neurons connected within a network can alter their firing rates to remain at the optimal level. However, the connections between neurons are also plastic, meaning they can be changed. Learning, for example, can strengthen some connections while weakening others. How does a neuronal network retain homeostasis in the face of these changing connections? In his colloquium, Dr. Hengen discussed his work examining network homeostasis following experience and learning.

In a highly interconnected neuronal network with recurrent excitation and feed forward/feedback inhibition, small changes in connectivity will rapidly undermine stability. Synapse specific plasticity mechanisms such as long-term potentiation and long-term depression (involved in learning and development) introduce positive feedback into networks that, unaccounted for, are predicted to result in hyper- or hypo-excitability. It has been suggested that homeostatic mechanisms measured in cell culture and acute slice preparations may maintain stable circuit function by keeping neuronal firing within a set point range. However, such firing rate homeostasis has never been demonstrated in the intact animal. Dr. Hengen discussed data collected during chronic multielectrode recordings to monitor firing rates in the primary visual cortex of freely behaving rats during monocular visual deprivation (MD). Firing rates in visual cortex were suppressed over the first two days of MD, but then rebounded to baseline over the next two to three days, despite continued MD. This drop and rebound in firing was accompanied by bidirectional changes in synaptic strength measured in acute slices. The rebound in firing was independent of sleep/wake state but was cell-type specific, as inhibitory interneurons and pyramidal neurons responded to MD with different time courses. These data establish that homeostatic mechanisms within the intact central nervous system act to stabilize neuronal firing rates in the face of sustained sensory perturbations. Dr. Hengen's presentation also offered insight into ongoing work that aims to connect the molecular mechanisms of homeostatic plasticity with animal behavior. These experiments will offer a novel understanding of the relationship between the external environment and the molecular determinants of our brain function.

Lina Ni, PhD
Department of Biology
Brandeis University

A gustatory receptor paralogue controls rapid warmth avoidance in *Drosophila*

Those who believe humans have a sixth sense are correct, but it is not a psychic ability. Our sixth sense is thermosensation, which helps us regulate our body temperature, avoid danger and, for some species, detect prey. Certain proteins and their receptors, known as thermosensors, can allow animals to exhibit preferences for one temperature or another. However, the molecular processes behind thermosensors are not fully understood. In her colloquium, Dr. Ni discussed her work examining the molecular underpinnings of temperature preference and avoidance behaviors in the fruit fly Drosophila*.*

Behavioral responses to temperature are critical for survival, and animals from insects to humans show strong preferences for specific temperatures. Preferred temperature selection promotes avoidance of adverse thermal environments in the short term and maintenance of optimal body temperatures over the long term, but its molecular and cellular basis is largely unknown. Recent studies have generated conflicting views of thermal preference in the fruit fly, *Drosophila*, attributing importance to either internal or peripheral warmth sensors. Here Dr. Ni helps to reconcile those views by showing that thermal preference is not a singular response, but involves multiple systems relevant in different contexts. Dr. Ni and colleagues previously found that the transient receptor potential channel TRPA1 acts internally to control the slowly developing preference response of flies exposed to a shallow thermal gradient. Dr. Ni now reports that the rapid response of flies exposed to a steep warmth gradient does not require TRPA1; rather, the gustatory receptor GR28B(D) drives this behavior through peripheral thermosensors. Gustatory receptors are a large gene family, widely studied in insect gustation and olfaction, and are implicated in host-seeking by insect disease vectors, but have not previously been implicated in thermosensation. At the molecular level, GR28B(D) misexpression confers thermosensitivity upon diverse cell types, suggesting that it is a warmth sensor. These data reveal a new type of thermosensory molecule and uncover a functional distinction between peripheral and internal warmth sensors in this tiny ectotherm, reminiscent of thermoregulatory systems in larger, endothermic animals. The use of multiple, distinct molecules to respond to a given temperature, as observed here, may facilitate independent tuning of an animal's distinct thermosensory responses.

Volen Center for Complex Systems Poster Session

The Volen Retreat offers the opportunity for all Volen-affiliated faculty, postdoctoral fellows and graduate students to present a poster detailing their research. This is an important opportunity for other members of the community to engage with their fellow scientists and exchange ideas. The face-to-face format of a poster session allows for direct and detailed discussion of data and techniques. This past year, 29 graduate students and postdoctoral fellows presented posters at the Volen Retreat. The presenters and titles are listed below.

Presenter	Poster Title
Theodore Brookings	Fitting neuron models by minimizing control current
Bethany Christmann	The role of dorsal paired medial neuron and mushroom body interaction in the memory consolidation circuit in *Drosophila*
Jaime Devine	Why do you nap? Influences of sleep behavior and napping on mental and physical health
Yasmin Escobedo Lozoya	Altered balance of excitation and inhibition in an *in vitro* model of infantile spasm epilepsy
Veronica Flores	Effects of taste experience on conditioned taste aversion
Maria Genco	Homeostatic regulation of intrinsic excitability in *Drosophila* motor neurons
Amy Ghiretti	The GTPase Rem2 is a negative regulator of activity-dependent dendritic complexity
Marie Goeritz	*In vivo* network responses to temperature changes in the stomatogastric nervous system of the Jonah crab (*Cancer borealis*)
Patricia Goodwin	Regulation of sleep by microRNAs in *Drosophila*
Sara Haddad	Temperature and neuromodulation
Kyle Harrington	Brevis, a functional artificial life simulator

Volen Center for Complex Systems Poster Session (Cont.)

Paula Haynes	Sleep regulation by the DPM-alpha'beta' memory consolidation circuit in *Drosophila*
Anne Joseph	CaMKIV bidirectionally modulates synaptic and firing rate homeostasis in cortical neurons
Katelyn Kenny	Molecular mechanisms behind Rem2 activity regulation
Amanda Lash	The Bruner-Potter effect revisited: effects of age, hearing acuity and working memory on spoken word recognition
Chang Liu	Characterizing sleep of population flies by using *Drosophila* population monitor
Jacqueline McDermott	The effect of Sema4D on GABAergic synapse assembly
Aoife McMahon	A new tool for the identification of RNA binding protein targets within small numbers of discrete neurons
Anna Moore	Sema4D signaling in mammalian CNS GABAergic synapse development
Narendra Mukherjee	Palatability-related orofacial behaviors follow sudden ensemble firing rate transitions in gustatory cortex
Scott Neal	Sensory signal integration in the *C. elegans* dauer fate decision involves the nematode CaMKI/IV and neuropeptidergic signaling
Heather Panic	Vestibular and visual cues for dynamic balance
Lisa Payne	Attention-modulated alpha-band oscillations protect against intrusion of irrelevant visual and auditory stimuli
Aram Raissi	The role of Semaphorin 4D on GABAergic synapse formation and epileptogenesis in the mammalian hippocampus
Chad Rogers	Misleading contexts: age-related changes in listening flexibility and the false hearing effect
Honi Sanders	Is hippocampal rate remapping reconcilable with phase precession?
Asuka Takeishi	Mechanisms of starvation dependent plasticity in thermotaxis behaviors in *C. elegans*
Vedakumar Tatavarty	Regulation of synaptic AMPA receptor turnover underlies synaptic scaling down
Yanxun Yu	Remembering the environment: CaMKI mediates long-term temperature memory in *C. elegans*

The M.R. Bauer Summer Science Research Fellow

The M.R. Bauer Summer Science Research Fellowship Program was inaugurated in summer 2014. The M.R. Bauer Foundation generously supported an undergraduate's research project: Brandeis undergraduate Kelly Flavahan '15 was able to perform research in the laboratory of Volen Center for Complex System's faculty member Steve VanHooser. This opportunity allowed a very talented undergraduate to tackle an important question in brain development. This summer experience will form the basis of Ms. Flavahan's senior thesis.

Ms. Flavahan's work was aimed at understanding the way brains make functional systems. During development, brain circuits are assembled through processes that require both genes and sensory experience. Abnormal genes or abnormal sensory experience early in life have profound and permanent impact on neural development. In a high-throughput screen for genes that might be involved in the experience-dependent development of the cortex, the laboratory of Suzanne Paradis, another member of the Volen Center, identified the gene Rem2 as necessary for proper dendritic branch length and for the development of synaptic contacts in an *in vitro* culture system. During the summer of 2014, she examined whether modifying Rem2 could alter the development of neural circuits in living animals. Ms. Flavahan was part of a two-person team (along with a graduate student) that discovered that Rem2 knock out mice — that is, mice in which the Rem2 gene had been genetically deleted — do not exhibit normal ocular dominance plasticity in visual cortex. As a part of these experiments, Ms. Flavahan learned to use advanced imaging tools like 2-photon microscopy and fluorescent calcium indicator dyes in order to watch — in intact, living animals — the activity of hundreds of neurons responding in real-time to visual stimulation. These experiments suggest 1) that Rem2 activity is modulated by the levels of activity/experience that are found in living animals, and 2) that Rem2 has a major influence on the experience-dependent construction of functional circuits during brain development. Ms. Flavahan will continue to develop this project through her senior year.

Acknowledgments

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

We especially acknowledge Kim MacKenzie, a recent PhD graduate from the neuroscience program, for her valuable contributions and editorial assistance in the preparation of this 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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