Brandeis University

Benjamin and Mae Volen National Center for Complex Systems

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

The M.R. Bauer Foundation Colloquium Series, Distinguished Lecturer Series, Annual Scientific Retreat, and Summer Science Research Fellowship 2015-16 Summary

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The 2015-16 M.R. Bauer Foundation Colloquium Series, Distinguished Lecturer Series, Annual Scientific Retreat, and Summer Science Research Fellowships

Introduction

A scientist's career is often sparked by serendipity. Inspired by a chance meeting, a seemingly fleeting moment, or a happenstance encounter with the world, a young person decides to leap into the universe of scientific knowledge.

It is at this critical moment that we must seize them, to ensure that this inspiration is nourished and sustained.

The magic of science alone cannot hold hearts and minds. Stories of brilliance and genius can be intimidating to unseasoned scientists. Left to question their talents or compare accomplishments, students can become self-doubting. They do not hear about the frustrations that mar every investigation. They are not privy to those conversations when a researcher asks a colleague for help. In other words, they lack the rounded perspective that comes from maturity and experience.

It is our obligation to serve this generation of neuroscientists with wisdom, patience, and understanding. Once students arrive on campus and in the lab, our responsibility is to assist them in navigating the practice and the profession — and to constantly reinforce their (and our) reasons for joining the neuroscience community. Doing so will make intentional what is inspirational, and will continually renew their commitment to the field.

If the research we talk about here is to grow, then we need these aspirants to carry the torch. Our mentees, research assistants, postdocs — the future of neuroscience, many of whom join us in these conversations — crave guidance and perspective, even when they do not actively seek it out. Neuroscientists work hard, overcome extraordinary challenges, and take succor in fresh ideas and methods. Discovery, they will learn, is a destination that often takes decades to reach.

All of this is remarkable because the M.R. Bauer Foundation, the longstanding benefactor of the Colloquium, Lecture Series, and Annual Retreat, has raised the stakes in how Brandeis trains emerging scientists. A generous, multiyear gift for summer undergraduate research fellowships will ensure that 50 more students participate in intensive research under the tutelage of our esteemed faculty. The M.R. Bauer Foundation recognizes that educating young scientists is of equal measure to the professional development offered to us through these events.

Neuroscience is revelatory. With a little luck and a lot of hard work, aspiring students, my Brandeis colleagues, and everyone in the field will continue to find the inspiration that drives discovery.

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

The M.R. Bauer Foundation Colloquium Series Summaries

Introduction

No man is an island, and no neuron works alone. To perform the multitude of processes necessary for learning and behavior, networks of neurons must connect both locally and across the brain. Synapses, the area where a message is relayed from one neuron to the next, must have the proper balance of proteins. Neurotransmitters, the chemical messengers of the brain, must be released in the right order and at the right concentrations. Neural circuits that underlie the constant activity of the brain must be kept on an even keel.

The neural circuits of the brain perform myriad functions, from building spatial representations gathered by whiskers in rats to keeping track of temporal information in humans. In order to adapt to shifting environments, the brain must have methods of retaining a balance in function, or homeostasis. Why the need for such control? Abnormalities in the development or activity of neural circuits are implicated in disorders from autism to epilepsy. And an understanding of how neural circuits develop, form, and remain balanced can pave the way to new treatments.

The 2015-16 M.R. Bauer Foundation Colloquium Series explored new developments in the understanding of the networks of the brain: how they form, how they function, and how they maintain balance in the face of an ever-changing environment. Nine distinguished scientists offered unique insights into the process of developing brain networks and homeostasis, whether at the level of proteins at the synapse or entire networks of neurons. Each speaker has presented a summary of his or her work, which is preceded by a brief introduction set in italics, explaining the presentation in a more general framework of synaptic transmission in the face of a plastic, changing brain.

Takao Hensch
Professor of Molecular and Cellular Biology
Department of Molecular and Cell Biology
Harvard University
(November 3, 2015)

Balancing Plasticity/Stability Across Brain Development

What if autism could be reversed in adulthood? Developmental disorders are often due to disruptions during key developmental periods, called critical periods. Abnormal development during critical periods currently leads to behavioral, functional and cognitive problems down the road. But what if it doesn't have to be that way? The Hensch lab is examining the molecular processes behind critical periods and methods to reopen them later in life. By reopening a critical period, it may be possible to treat altered brain development or repair damage due to a brain injury.

During development, different brain systems exhibit transient periods of heightened plasticity, referred to as "critical periods," that allow children to rapidly acquire sensory, motor, cognitive, and language skills. Disruption of these critical periods early in life can have profound developmental consequences. For instance, subtle differences in phoneme discrimination in the first year of life are associated with varying levels of vocabulary development years later. Recent progress, primarily in the developing visual system, has begun to unravel the biological basis of this critical period timing.

Crucially, the onset and time-course of these windows of opportunity and vulnerability are governed by the actions of GABAergic interneurons. Manipulation of parvalbumin-positive (PV+) interneurons in particular, through genetic or pharmacological disruption, can prematurely trigger or delay critical period opening — effectively dissociating critical periods from chronological age. Conversely, novel molecular regulators of neuromodulatory systems or perineuronal nets in the extracellular matrix surrounding PV+ cells actively dampen plasticity beyond the critical period to maintain circuit stability. Lifting these "brakes" in adulthood can reopen juvenile levels of brain plasticity.

In other words, critical period timing is itself plastic. These results carry striking implications for humans. Genetic or environmental risk factors, such as drug exposures, will effectively shift the normal trajectory of brain development. For example, gestational exposure to serotonin reuptake inhibitors is associated with premature closure of a critical period for phoneme discrimination. In mouse models of autism spectrum disorders, altered PV+ circuit maturation leads to accelerated or delayed critical period timing, which may, in part, underlie the emergent cognitive dysfunction. In turn, circuit-based strategies can now be leveraged for treating brain injury or correcting aberrant development in adulthood.

Ivan Soltesz
Professor of Neurosurgery and Neurosciences
Neurosurgery Department
Stanford University School of Medicine
(November 24, 2015)

Organization and Control of Hippocampal Circuits

Neurons do not work alone. Individual neurons and interneurons are small parts of larger networks, and the carefully timed firing of neurons in a network form the basis of rhythms and functioning of the brain. The interneurons play their part by inhibiting the firing of other neurons, controlling the activity patterns and rhythms that control behavior. In his talk, Dr. Soltesz discussed his work examining the interneurons of the hippocampus. An understanding of how these networks are organized can and has led to methods of altering the firing patterns, increasing the possible ways for treating epilepsy and other disorders of network function.

Since the time of the early pioneers of neuroscience, a highly effective approach toward studying brain networks has been to focus on its cellular elements, the distinct neuronal subtypes. In the case of inhibitory interneurons within the hippocampus — a brain structure known to play key roles in certain forms of learning and memory as well as in a variety of brain disorders — research aimed at reconstructing the neuronal machine from its diverse cellular elements revealed that distinct interneurons form synapses only with certain specific parts of the postsynaptic cells, such as the initial segment, cell body, proximal or distal dendrites. For example, chandelier (axo-axonic) cells release the inhibitory neurotransmitter GABA selectively onto the axon initial segments of the excitatory pyramidal cells, whereas basket cells innervate the cell body and the proximal dendritic region, and still other interneuron types are specialized to form synapses exclusively on distal dendrites. Because the different subcellular domains of neurons serve different roles, the selective innervation patterns of interneuronal types reflect a remarkable functional division of labor. More recently, it has been recognized that, in addition to the subcellular, spatial specificity of the individual interneuronal subtypes, there is also a great deal of temporal specificity. For example, chandelier cells, basket cells and the dendritically projecting interneurons release GABA at different times during behaviorally relevant network oscillations such as the theta rhythm or sharp wave ripples. This closely inter-twined spatio-temporal specificity of neuronal network organization is captured by the term "chronocircuitry."

In my talk, I discussed new results regarding chronocircuit organization and control in the hippocampus. First, concerning spatial specificity, I showed new data that demonstrate that interneurons do not generate a homogenous or "blanket" inhibition as previously thought, but they form highly specific subcircuits with specific types of pyramidal cells, creating asymmetric inhibitory interactions between separate output channels from the hippocampus. Second, regarding the temporal aspects of chronocircuit organization, I presented evidence for overarching "meta" rules for subtype-specific firing, for example, in the form of frequency-invariant temporal ordering of the firing of basket cells and dendritically projecting cells. Third, I showed that neuromodulatory processes also fit into the newly recognized heterogeneity of hippocampal microcircuits. For example, we recently recognized that cannabinoid modulation of certain ion channels called HCN channels selectively occurs in a precisely defined subset of hippocampal pyramidal cells. New insights into circuit organization are increasingly made possible by sophisticated high-throughput techniques that generate cell type-specific data on neuronal circuits with unprecedented detail, accompanied by rapid increases in computing power. In the fourth part of my talk, I discussed our efforts to construct strictly data-driven, full-scale (1:1) computational models of the hippocampus in order to gain quantitative insights into the roles of the various constituent cell types in chronocircuit operations. These full-scale models are being used to test specific mechanistic hypothesis — for example, concerning the role of basket cells in the generation of the hippocampal theta rhythm. In addition, I also discussed the possibility to rationally derive simpler computational models that can be run on personal computers from the full-scale models. Finally, I presented recent results to show that it is now possible to control abnormal chronocircuit behavior — for example, in experimental temporal lobe epilepsy, using on-demand optogenetic interventional strategies. These new closed-loop optogenetic approaches offer the possibility to intervene in malfunctioning chronocircuits with unparalleled spatial, temporal and cell type-specificity.

Work in my laboratory is funded by the NIH, NASA and NSF.

Graeme Davis
Department of Biochemistry and Biophysics
Programs in Neuroscience, Cell Biology and Developmental Biology
University of California, San Francisco
December 8, 2015

The Stable Brain: Homeostatic Control of Neural Function

A stable brain is a happy brain. Chemicals in the brain, the neurotransmitters, are charged with the Herculean task of maintaining homeostasis, or balance, in the functions of the brain. But how can the brain maintain homeostasis over a lifetime of changes? Dr. Davis and his lab examine the basic mechanisms that allow for homeostasis in brain circuits. In his talk, he discussed his work focusing on genetic mutations that may disrupt the processes of homeostasis, such as the release of chemical messengers that control the timing and firing of neurons.

The brain is astonishing in its complexity and capacity for change. This has fascinated scientists for more than a century. But, a paradigm shift is underway. It seems likely that the plasticity that drives our ability to learn and remember can only be meaningful in the context of otherwise stable, reproducible, and predictable baseline neural function. Without the existence of potent mechanisms that stabilize neural function, our capacity to learn and remember would be lost in the chaos of daily experience-dependent change. This underscores two great mysteries in neuroscience. How are the functional properties of individual neurons and neural circuits stably maintained throughout life? And, in the face of potent stabilizing mechanisms, how can neural circuitry be modified during neural development, learning and memory? We are seeking to answer to these questions by harnessing the powerful forward genetic tools of *Drosophila* and translating our findings into studies of the mammalian nervous system.

The mechanisms that stabilize neural function throughout life can be described as homeostatic. It has become clear that homeostatic signaling systems act throughout the central and peripheral nervous systems to stabilize the active properties of nerve and muscle. Evidence for this has accumulated by measuring how nerve and muscle respond to the persistent disruption of synaptic transmission, ion channel function, or neuronal firing. In systems ranging from *Drosophila* to human, cells have been shown to restore baseline function in the continued presence of these perturbations by rebalancing ion channel expression, modifying neurotransmitter receptor trafficking, and modulating neurotransmitter release. In each example, if baseline function is restored in the continued presence of a perturbation, then the underlying signaling systems are considered homeostatic.

A major goal of my laboratory is to define the cellular and molecular mechanisms that achieve the homeostatic control of presynaptic neurotransmitter release. This was the focus of my seminar. In brief, we are pursuing the first electrophysiology-based forward genetic screen for mutations that specifically disrupt the homeostatic modulation of synaptic transmission *in vivo*. I presented the most recent advances from our genetic studies. In doing so, I also discussed the bi-directional nature of the homeostatic signaling systems that control presynaptic neurotransmitter release, how bi-directional signaling is achieved at a cellular level, and new emerging molecular mechanisms.

Diana Bautista
Associate Professor of Cell and Developmental Biology
Department of Molecular and Cell Biology
University of California, Berkeley
(November 10, 2015)

Itchy and Scratchy: Molecular Mechanisms of Acute and Chronic Itch

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Is there anything more annoying than an itch in a place you can't quite reach? But why do we itch? At times it is beneficial, such as when it is a cue to swat away the mosquito before it gets much of a bite. But in some, the itch becomes chronic, for uncertain reasons. Dr. Bautista and her lab are working to identify the processes that underlie chronic itch, the first step in determining new treatments or cures. Her work in mice genetically modified to have chronic itch has found a first candidate, a serotonin receptor, which could be a target for future treatments.

Humans rely on the sensations of itch, touch, and pain for a broad range of essential behaviors. For example, acute pain acts as a warning signal that alerts us to noxious mechanical, chemical, and thermal stimuli, which are potentially tissue damaging. Likewise, itch sensations trigger reflexes that may protect us from disease-carrying insects. In addition, during inflammation or injury, we experience a heightened sensitivity to touch that encourages us to protect the injured site. Despite these essential protective functions, itch and pain can outlast their usefulness and become chronic. In mammals, these sensations are mediated by specialized subsets of somatosensory neurons that innervate the skin and viscera. Non-excitable cells, such as keratinocytes and immune cells, also work in conjunction with somatosensory neurons to promote and maintain acute and chronic inflammatory pain and itch. My lab aims to identify the mechanisms by which these cell types detect itch and tactile stimuli, under normal and pathophysiological conditions. We use a combination of cellular physiology, molecular biology, molecular genetics, and behavioral studies to probe the cellular and molecular mechanisms that mediate itch, touch, and pain. We recently examined the natural variation across genetically distinct mouse strains to identify transcripts co-regulated with itch behavior. This survey led to the discovery of a plethora of candidate itch transducers in skin, sensory neurons, and immune cells. We have shown that one such candidate, the serotonin receptor HTR7, is a key mediator of acute and chronic itch. Abberant serotonin signaling has long been linked to a variety of human chronic itch conditions, including atopic dermatitis. But the serotonin receptor subtypes that mediate chronic itch remained enigmatic. In a mouse model of atopic dermatitis, we have now shown that mice lacking HTR7 displayed significantly reduced itch-evoked scratching, inflammation, and skin lesion severity. These data highlight a role for HTR7 in acute and chronic itch, and suggest that HTR7 antagonists may be useful for treating a variety of pathological itch conditions.

Erin Schuman
Managing Director
Max Planck Institute for Brain Research
(March 8, 2016)

Local Control Mechanisms at Neuronal Synapses

Messages are sent from one neuron to the next at the synapse (the junction where two neurons meet). Proteins located at the synapse control how that synapse functions. Any alterations in the levels of these different proteins can affect the activity of the neuron. What processes are in place to help neurons maintain the correct protein levels, and how does the synapse adjust when those levels are out of normal range? Dr. Schuman discussed the work of her group examining the functioning of the synapse, and how the individual neuron can control the proteins found in the synapse. They have developed imaging technologies that allow them to visualize newly formed proteins, in order to better understand how the neuron maintains a balance of protein levels.

The brain generates representations of environmental inputs received from sensory systems and must maintain and update these representations to allow humans and other animals to effectively interact with the environment. Brain cells, or neurons, connect and communicate at structures called synapses. Each neuron possesses about 10^4 synapses. Synapses are packed with over 500 different proteins that exist in copy numbers of ~20 to 2000 molecules per synapse. The proteins present at a given synapse determine how that synapse functions. When the brain adapts, such as during learning and memory, the properties of neurons and synapses change to encode and maintain new information. The adaptive response of neurons and synapses relies on modifications to existing proteins as well as changes in gene transcription, protein synthesis, and protein degradation. To endow synapses with independent control over their protein composition, neurons have delivered the cell biological machines for protein synthesis and degradation to synapses.

The Schuman lab is interested in understanding how synapses work. In particular, we focus on how an individual neuron controls the type, amount, and location of the proteins that populate its synapses. Research over the past 20 years or so has led to the identification and a basic functional understanding of the proteins that populate synapses. In order to understand how all of the proteins function together and maintain their concentrations in the appropriate range one must obtain quantitative information at high resolution. What are the populations of RNA molecules that code for protein (mRNA) and regulate synaptic function? What is the density of molecules in neurons? What is the lifetime of the different mRNAs and proteins at synapses? How do these numbers relate to the strength of individual synapses? How are these numbers altered during synaptic plasticity, and what effect does this have on the network of synaptic proteins? How do these molecular processes contribute to learning and memory in animals? These are the types of questions that we seek to answer with a combination of imaging, electrophysiology, biochemistry, molecular biology, bioinformatics, modeling, and behavioral analyses.

The Schuman group develops and uses advanced technologies (deep sequencing of neuronal mRNA 3'UTRs; fluorescent labeling and quantification of individual mRNAs; high-resolution in situ hybridization; labeling, identification, and visualization of newly synthesized proteins in identified neurons) to uncover the local cell biological mechanisms that allow synapses to function autonomously and be modified by experience. In order to identify or visualize recently synthesized proteins, we (together with Dave Tirrell at Caltech) developed a new suite of methods (BioOrthogonal NonCanonical Amino acid Tagging, or BONCAT) that use a non-canonical amino acid (NCAA), modeled after a natural amino acid, such as methionine. The NCAA is close enough in structure that the cellular protein synthesis machinery is "fooled" and uses the NCAA, instead of a natural amino acid, to make new proteins. Moreover, the NCAA has a special chemical group that serves as a molecular handle — allowing us to access to the newly synthesized protein — to identify it with mass spectrometry or to tag it with a fluorescent dye and visualize it within a neuron. Taken together, these technologies allow us and other researchers to unravel the molecular mechanisms that underlie synaptic protein homeostasis. Interestingly, several developmental (e.g. Fragile X Mental Retardation Syndrome) and degenerative (e.g. Parkinson's disease) neural disorders appear to target the machinery that maintains synaptic proteins in a dynamic range — highlighting the importance of these local control mechanisms.

Dean Buonomano
Professor
Department of Neurobiology
Brain Research Institute
University of California, Los Angeles
(March 15, 2016)

The Neural Basis of Timing and Temporal Processing

As children, we learn to jump rope, carefully timing our next jump to the expected time it will take for the rope to make another revolution. But how does the brain keep track of temporal information, such as how long it might take the rope to make it back to our feet? Rather than a small clock residing in one particular brain area, Dr. Buonomano discussed the role of recurrent activity in networks of neurons as a method of "time-keeping." His lab has demonstrated that even neurons in a slice of brain in a dish can learn to "tell" time based on a temporal pattern. The recurring activity within the network can lend to the anticipation of a future, expected event.

The brain's ability to seamlessly assimilate and process temporal information is critical to most behaviors, from understanding speech to anticipating events such as when a traffic light will change colors. Because timing and temporal processing represent a fundamental neural computation, we postulate that there is no single brain area responsible for timing but rather that most neural circuits are intrinsically able to process temporal information on an as-needed basis.

We have proposed that most forms of timing bear little resemblance with man-made clocks and, rather, rely on the neural dynamics of recurrent neural networks. Specifically, that sensory timing (e.g., interval discrimination) emerges from interaction of the time-varying internal state of neural networks with external stimuli. The internal state is defined not only by ongoing activity (the active state) but by time-varying synaptic properties, such as short-term synaptic plasticity (the hidden state). Psychophysical support for this hypothesis was presented.

In contrast to sensory timing, motor timing requires networks to actively generate responses, and thus rely on self-perpetuating activity within neural networks. It has been proposed that motor timing emerges from the dynamics of balanced recurrent neural networks. But a long-standing limitation of this theory is that the relevant regime is chaotic. We show that it is possible to tame chaos in firing rate recurrent networks, by tuning the recurrent weights. Within this framework, networks store spatiotemporal objects (such as handwritten words) as the voyage through phase space — as opposed to the destination (i.e., a fixed point attractor). One prediction of the theory that timing is an intrinsic property of neural networks is that even *in vitro* cortical slices may be able to "learn" to tell time. We provide support for this prediction by demonstrating that intervals chronically presented to cortical circuits through optogenetic stimulation can "learn" simple temporal patterns.

The M.R. Bauer Foundation Distinguished Guest Lecturer Series

Introduction

Every year, the M.R. Bauer Foundation Distinguished Lecturer program brings to campus two distinguished visitors who spend a full week at Brandeis. These weeklong 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 Marla Feller and Daniel Feldman from University of California, Berkeley, and Liqun Luo from Stanford University, who also served as the keynote speaker for the Volen National Center for Complex Systems Scientific Retreat 2015. Dr. Luo's seminar summary will be found in the Volen Retreat 2015 section.

Marla Feller
Professor of Neurobiology
Department of Molecular and Cell Biology and Helen Wills Neuroscience Institute
University of California, Berkeley
(March 28, 2016)

Wiring Up a Circuit to Perform Computations: Development of Direction Selectivity

During development, neurons form circuits with other neurons. These circuits form the basis of brain function. A basic question in neuroscience research, therefore, is how these circuits are formed. How do neurons know to wire with other neurons to perform different functions? Is it based on genetics? In her lecture, Dr. Feller discussed her work examining the wiring of networks in the retina of the eye. Certain neurons in the retina respond to images that move in specific directions. Her lab has found that the activity of these neurons is not only determined by genetics but also by activity. They hypothesize that experience during development directs the retinal neurons to respond to certain stimuli and form circuits, and that genetics is only part of the answer.

How are circuits wired up during development to perform specific computations? We address this question in the retina, which comprises multiple circuits that encode different features of the visual scene, culminating in roughly 20 different types of retinal ganglion cells. Direction-selective ganglion cells (DSGCs) respond strongly to an image moving in the preferred direction and weakly to an image moving in the opposite, or null, direction. Direction-selective ganglion cells are critical for driving ocular-motor reflexes that stabilize images on the retina as we move through a visual scene as well as for sensing the movement of objects within the visual scene.

In adult retina, the preferred directions of DSGCs are not randomly distributed but cluster along distinct directions (up, down, left, and right), which we refer to as cardinal axes. The mechanisms that guide the emergence of these cardinal directions and the precise excitatory and inhibitory connectivity that define them are unknown. Work from our lab and others has demonstrated that direction selective responses are detectable at the age of the earliest visual responses, indicating that the retinal circuitry mediating direction selectivity emerges prior to normal visual experience, and these responses remain after a variety of genetic and pharmacological blockades of synaptic signaling in the early retina. Hence the primary hypothesis has been that direction selective circuits emerge independent of neural activity.

I present recent results from my laboratory that counters this hypothesis and demonstrates that both activity-dependent and independent mechanisms underlie the development of retinal direction selectivity.

Daniel Feldman
Professor of Neurobiology
Department of Molecular and Cell Biology and Helen Wills Neuroscience Institute
University of California, Berkeley
(March 28, 2016)

Sensory Maps and Homeostasis in Whisker Somatosensory Cortex

Aside from being excellent tools for tickling humans, animal whiskers are highly sensitive to the sensory world. Sensory inputs from the whiskers can help an animal build a mental representation of their environment, allow such feats as squeezing through small holes and remembering where to find the yummiest foods. As Dr. Feldman discussed, the neurons of the rodent sensory cortex are arranged in layers of highly organized circuits. His lab examines how these layers interact to maintain homeostasis, or balance, in the face of a changing environment. How do the networks change and maintain their activity level through processes such as learning or sensory deprivation? Dr. Feldman highlighted the role of interneurons in maintaining homeostasis in whisker sensory networks.

How do neural circuits in cerebral cortex encode and process sensory information, and learn and adapt to patterns in the sensory world? My lab studies these questions in the whisker map in rodent somatosensory cortex (S1), with emphasis on layer (L) 2/3, which contains a sparse and highly plastic whisker representation. We recently quantified the topography of the whisker map in L2/3 at cellular resolution using calcium imaging. We found pronounced salt-and-pepper intermixing of neurons tuned to different whiskers, in contrast to the common model of a smooth whisker map with homogeneous local tuning. L2/3 pyramidal cells projecting to different targets differentially sample this salt-and-pepper map, with more somatotopically accurate information being relayed to S2 (the likely pathway for form perception) than to M1. Some L2/3 neurons are tuned for complex multi-whisker stimuli, but how this is mapped in S1 remains unknown.

We also study circuit mechanisms for use-dependent map plasticity and homeostasis in S1. Cortical plasticity is a dynamic balance of Hebbian mechanisms that alter neural tuning in response to experience, and homeostatic mechanisms that actively maintain cortical firing rates. Whisker deprivation induces rapid homeostatic plasticity that preserves sensory responsiveness and precedes classical changes in receptive fields and maps. The most rapid homeostasis occurs with one day of deprivation and is mediated by disinhibition of pyramidal cells. This occurs through rapid regulation of parvalbumin (PV) interneuron circuits, including both feedforward and recurrent inhibitory networks in L2/3. We identified several sites of plasticity within L2/3 PV networks that mediate homeostatic disinhibition following sustained whisker deprivation. In ongoing work, we show that the most rapid disinhibition is mediated by reduced intrinsic excitability of PV neurons.

These findings support a growing body of evidence that PV interneurons are a critical nexus for homeostatic plasticity in sensory cortex. This single site of plasticity can control average firing rate in local cortical networks, regulate sensory gain, and gate subsequent Hebbian plasticity for reorganization of the whisker map. We find that feedforward inhibition in L2/3 is strongly impaired in several genetically distinct transgenic mouse models of autism, suggesting that dysregulation of inhibitory homeostasis may be a common factor for this disorder.

The Volen National Center for Complex Systems Scientific Retreat 2015

Introduction

The Volen National Center for Complex Systems held its annual scientific retreat on October 5, 2015. This year's theme was "Dynamics of Complex Systems." Liqun Luo of Stanford University was our keynote speaker, and he wrapped up the day with his seminar about olfactory systems. Faculty, postdoctoral fellows, and students alike traveled off campus to the New England Aquarium in Boston. Holding the retreat away from campus encourages the scientists to interact away from their familiar surroundings and fosters communication and connections that lead to interdisciplinary and innovative collaborations — collaborations that are far less likely to occur during the normal bustle of day-to-day life in the laboratory.

In addition to the keynote speaker, we had four Brandeis postdoctoral fellows' presentations. Trish Goodwin from Leslie Griffith's lab, Viktor Horvath from Irv Epstein's lab, Phillip Rosenbaum from Eve Marder's lab, and Anna Moore from Suzanne Paradis's lab all presented their research stories to the Volen community. As the summaries that follow will make clear, the 2015 retreat offered a view of the amazing research being pursued at Brandeis. Each project brings a better understanding of the complex systems around us.

The Volen National Center for Complex Systems Scientific Retreat

Schedule

October 5, 2015

8:30 a.m.
Arrival

9:00 a.m.
Trish Goodwin, Griffith Lab
“MicroRNAs in Drosophila Sleep”

9:40 a.m.
Viktor Horvath, Epstein Lab
“Pulse-Coupled Chemical Oscillators: Experiments, Models, Theory”

10:20 a.m.
Phillip Rosenbaum, Marder Lab
“Robustness of Circuit Output as Revealed by Neuromodulators With Converging Actions”

11:00 a.m.
Anna Moore, Paradis Lab
“Novel Molecular Mechanism, the Activity-Dependent Gene Rem2, Underlying Visual Circuit Plasticity”

Noon
Lunch Break and Visit Aquarium Exhibits

2:00 p.m.
Poster Session

3:00 p.m.
Keynote Speaker
Dr. Liqun Luo, Stanford University
“Organization and Assembly of the Olfactory Systems”

4:00 p.m.
Departure

Liqun Luo, PhD
Professor
Department of Biology
Stanford University and Howard Hughes
Medical Institute
(October 5, 2015)

Organization and Assembly of the Olfactory Systems

Studying the human brain and its billions of neurons and synapses can be an overwhelming prospect. Studying smaller brains, such as the fruit fly or mouse, can offer insights into the development and function of the more complex human brain. Dr. Luo, in his two lectures, discussed methods of tracking neuronal connections between areas of the brain. His lab focuses on the olfactory system specifically, as a model of how the rest of the brain develops precise neuronal circuitry.

The human brain contains ~10^{11} neurons, each making ~10^3 synapses with other neurons. These 10^{14} synaptic connections enable us to sense, think, remember, and act. How is this vast number of neurons organized into circuits to process information? How are these circuits assembled during development? To address these questions, we use model neural circuits in the less numerically complex brains of the fruit fly (~10^5 neurons) and mouse (~10^8 neurons) and combine state-of-the-art molecular genetics and viral techniques with physiological and behavioral approaches.

Recent advances in neuroscience have produced an impressive array of tools to genetically label, anatomically trace, physiologically record, and functionally perturb specific populations of neurons. However, these methods are mostly applicable to studying local circuits of neurons; information about their long-distance connections is lost. A bottleneck in understanding the brain is to decipher the global patterns of neuronal connectivity. In the first talk, I described our recent development of viral-genetic tracing tools that enable systematic mapping of input, output, and input-output relationships of specific neuronal types in defined brain regions at the scale of the entire mouse brain. I used the locus coeruleus norepinephrine neurons and ventral tegmental area dopamine neurons as two examples to illustrate the utility of these methods in deciphering the circuit architecture of these key neuromodulatory systems.

The olfactory circuits of flies and mice share remarkable similarities and offer salient advantages for investigating their structure, function, and development. In the fly, olfactory receptor neurons (ORNs) expressing the same odorant receptor project their axons to the same glomeruli in the antennal lobe. Projection neurons (PNs) send dendrites to individual glomeruli and relay olfactory information via their axons to higher-order centers that mediate learned and innate olfactory behavior. The assembly of the fly olfactory system requires precise glomerular targeting of axons from each of the 50 ORN types and dendrites from each of the 50 PN types.

In the second talk, I focused on how wiring specificity is established during the assembly of the fly olfactory circuit. We found that PN dendrites pattern the antennal lobe prior to ORN axon arrival. Global graded cues and local binary determinants collaborate to pattern PN dendrites. ORN axon targeting also employs a multistep process involving trajectory choice, axon-axon repulsion, and synaptic partner matching to establish one-to-one connections between cognate ORNs and PNs. The molecules and mechanisms used in the assembly of the fly olfactory circuit are likely generally used in different circuits and organisms from insects to mammals.

Trish Goodwin, PhD
Postdoctoral Associate
Department of Biology
Brandeis University
(October 5, 2015)

MicroRNAs in *Drosophila* Sleep

As anyone who has experienced jet lag can attest, the body can go without sleep for only so long. Eventually you crash and sleep for 12 or more hours in one night. What signals your body to do this? Dr. Goodwin is examining the molecular processes behind this "rebound sleep," or the body's method of regaining balance in the sleep/wake cycle. In her talk, she discussed her work with Drosophila *(fruit flies), looking for particular spots in the genetic code necessary for controlling how and when we sleep.*

Sleep is a highly conserved behavior that is essential for brain function, but the molecular machinery that controls sleep is poorly understood. Changes in sleep/wake status are accompanied by changes in gene expression. One mechanism that may control these changes is microRNA-mediated suppression of mRNA translation. MicroRNAs (miRs) are small, 22 nucleotide-long non-coding RNAs that bind to the 3' UTRs of mRNAs and prevent their translation. Studies of sleep in mammals and circadian behavior in *Drosophila* suggest that miRs play a role in sleep and circadian clock output, but the role of miRs in sleep has not been studied systematically. Our research seeks to identify and characterize miRs that regulate sleep by employing miR sponges to inhibit specific miRs in the *Drosophila* genome. Sponges contain tandem repeats of miR target sequence, which prevent miRs from binding to their endogenous targets. To identify the maximum number of miRs that affect sleep, we have initially expressed sponges ubiquitously using TubulinGal4 and have begun screening these flies for changes in baseline sleep and sleep homeostasis. Sleep homeostasis is the ability to detect low levels of sleep and subsequently produce a compensatory increase in sleep (called "rebound sleep"). Out of 81 miRs screened thus far, we have identified 32 miRs that affect sleep. We found that the majority of miR sponges with effects on sleep cause decreases in sleep (n=23), while a minority of sponges cause increases in sleep (n=7). We have also identified 4 miRs that regulate the sleep homeostat (i.e. rebound sleep). Half of these affect rebound sleep specifically, while the other half affect both baseline and rebound sleep. Additionally, we investigated whether changes in sleep can cause changes in miR expression in *Drosophila*. We used nCounter miRNA expression assays (Nanostring Tech.) to compare miR expression after: (1) normal nighttime sleep, (2) 12 hours of nighttime sleep deprivation, (3) normal daytime waking, and (4) 12 hours of rebound sleep following nighttime sleep deprivation. We identified 16 miRs that undergo significant changes in expression with time of day or sleep deprivation (2-Way ANOVA). Of these 16 miRs, nine were found to have effects on sleep when we inhibited their function using sponges, four miRs had no change in sleep after inhibition, and three are undergoing testing. Future experiments will employ cell-type specific Gal4s and temporally restricted sponge expression (using $Gal80^{ts}$) to determine where miRs function and whether they function in adults or during development to regulate sleep.

Viktor Horvath, PhD
Postdoctoral Associate
Department of Chemistry
Brandeis University
(October 5, 2015)

Pulse-Coupled Chemical Oscillators: Experiments, Models, Theory

Like neurons, chemical reactions can oscillate. Depending on the concentrations, or strength, of the substances involved, the oscillations may display different behaviors. The behavior of chemical oscillators can give a unique look at the nature of a complex system, one that changes both with and in reaction to the substances it contains. Dr. Horvath described his work modeling the Belousov-Zhabotinsky oscillator. The model of oscillatory behavior he has developed is able to characterize how a pair of oscillators would function, based on the activity of one oscillator. This can have an impact on the modeling of oscillating neurons in the future.

Two identical pulse-coupled Belousov-Zhabotinsky (BZ) oscillators display various modes of synchronization as well as other interesting dynamical phenomena, like bursting and oscillatory death when their coupling strengths match. When the intrinsic frequencies of the two coupled oscillators initially match but the coupling strengths are unequal, this system may display a) phase locked oscillations, or b) stable temporal patterns where the frequencies of the oscillators no longer match (the peak alignments are fixed), or c) oscillator death. Similar behavior can be observed when the natural frequencies of the oscillators are significantly different and the coupling strengths are equal. Numerical simulations using a chemical model as well as in a phase model of the system show domains of various entrainment modes 1:1, 3:4, 2:3, 2:5, 1:2, 1:3, 1:4, etc., when the natural frequencies and/or the coupling strengths are varied. Here we demonstrate a method that enables us to find the combinations of the control parameters that produce a particular behavior. By using this method, we were able to characterize the collective behavior of a system of two BZ oscillators based on the dynamical features of a single pulse-perturbed BZ oscillator. This method is quite general and therefore it may be applicable to other systems where individual units that display oscillatory behavior are coupled via short pulses, such as networks of neurons.

Philipp Rosenbaum, PhD
Postdoctoral Associate
Department of Biology
Brandeis University
(October 5, 2015)

Robustness of Circuit Output as Revealed by Neuromodulators With Converging Actions

Neurons that are active, or firing, in sequence are said to be oscillating. Oscillating neurons are important for certain rhythmic behaviors, such as walking or, in the case of the crab stomach, the grinding action of teeth to chew food. Oscillating neurons depend on carefully balanced levels of chemicals, or neuromodulators, to maintain the rhythm of firing. Dr. Rosenbaum discussed his work examining how rhythms can be maintained even in the absence of some necessary neuromodulators. His work highlights how networks can maintain balance by increasing the amounts of some neuromodulators to compensate for the loss of others.

Motor circuit output for stereotypic movements has to be robust against external and internal perturbations. Both intrinsic neuronal properties and synaptic strengths are targets of neuromodulation. In the well-studied stomatogastric nervous system (STNS) of the crab *Cancer borealis*, the specific motor output generated by each neuromodulator depends on the subset of neurons affected.

Here we show that the modulators oxotremorine/pilocarpine, CabTRP1a, and red pigment concentrating hormone (RPCH) still elicit a form of the pyloric rhythm in the absence of action potentials in TTX, graded synaptic inhibition maintaining the underlying slow-wave. Proctolin, crustacean cardioactive peptide (CCAP), and TNRNFLRFamide do not evoke a pyloric rhythm in TTX. Interestingly, all of these modulators activate the same ionic conductance. Oxotremorine rhythms with and without TTX have a similar period — both are faster than in the front-end on condition. The slow wave membrane potential oscillations look similar to the regular pyloric rhythm without spikes. CabTRP1a elicits a rhythm with a longer period compared to the intact STNS, becoming even slower in TTX. The shape of the slow wave looks similar to the oxotremorine waveform. RPCH elicits a pyloric rhythm with a regular pyloric frequency, but in combination with TTX a very different activity pattern emerges. In LP most of the oscillations drastically decrease in amplitude and stay in pyloric frequency, but interposed with these are large amplitude slow oscillations (25-40s). This rhythm is mainly LP driven and PD receives strong LP inhibition. In the isolated pacemaker kernel, oxotremorine oscillations still persist in the PD neuron with the same frequency, whereas oscillations in CabTRP1a are only rarely observed with reduced frequency.

Our data suggests that neuromodulator activation of the pacemaker kernel and graded synaptic inhibition can restore rhythmic activity in the absence of action potentials.

Anna Moore, PhD
Postdoctoral Associate
Department of Biology
Brandeis University
(October 5, 2015)

Novel Molecular Mechanism, the Activity-Dependent Gene Rem2, Underlying Visual Circuit Plasticity

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Experience during development plays a major role in the formation of neuronal circuits. But levels of different proteins can also have a large effect on how the circuit develops. Activity in neurons can cause levels of different proteins to change, and can affect the formation of the circuit. In her talk, for example, Dr. Moore discussed her work with the molecule Rem2, without which a developing circuit of neurons in visual cortex cannot adapt to new circumstances. Without flexibility, a circuit cannot adapt to new sensory input and cannot function normally in an ever-changing environment.

The construction and adaptation of neuronal circuits is a carefully orchestrated series of events, which includes the formation of synapses and the morphogenesis of the dendritic arbor of individual neurons. These events are largely dependent on the relationship between spontaneous and experience-dependent activity and underlying intracellular signaling pathways. While changes in neuronal structure and function can occur on many levels, the identity of the molecules that link these changes in sensory experience to corresponding changes in intracellular signaling remains largely unknown.
We have identified a previously obscure Ras-like GTPase, Rem2 that has several hallmarks of being a major activity-dependent plasticity gene. For example, dialing Rem2 expression up or down in the context of neuronal activity positively regulates synapse formation while negatively regulating dendritic complexity. Further, Rem2 is a novel target of CaMKII, whereas phosphorylation of Rem2 by CaMKII regulates Rem2 subcellular localization and function.

In this talk, I focused on the novel role of Rem2 as an activity-regulated molecule required for neuronal plasticity in the visual system. In response to visual experience, changes in neural activity results in an upregulation of Rem2 expression in the visual cortex. In turn, Rem2 functions to set the intrinsic excitability of the neuron and promote synaptic scaling in response to occlusion of vision in one eye. As a result, in the absence of Rem2, mice are unable to exhibit ocular dominance plasticity, or the ability to shift the responsiveness from the closed eye to the open eye. Thus, Rem2 plays an important role in maintaining the nervous system's ability to adapt its neuronal network in response to changes in sensory input.

The Volen National Center for Complex Systems Poster Session

The Volen Retreat offers the opportunity for all Volen-affiliated faculty, postdoctoral fellows, and graduate and undergraduate students to present a poster detailing their research. This is an 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 year we saw a record number of posters: 40 postdoctoral fellows and students presented posters at the Volen Retreat. The presenters and titles are below.

Presenter	Poster Title
Daniel Acker	Semaphorin4D regulates GABAergic signaling in the intact hippocampus
Nicole Amichetti	A qualitative shift in comprehension strategies revealed under the triple challenge of age, reduced hearing acuity, and complex linguistic input
Eriko Atagi	Using cochlear implant simulations to examine the effects of signal degradation and linguistic complexity on sentence comprehension and listening effort
Belinda Barbagallo	Neural circuit control of physiological homeostasis in *Drosophila melanogaster*
Meredith Blankenship	Retronasal but not orthonasal presentation of odors is sufficient for learning in an olfactory preference task
Peter Bronk	Calcium/calmodulin regulation of the ether-a-go-go potassium cahannel
Mugdha Deshpande	Rerouting BMP receptor traffic suppresses synaptic growth defects in a *Drosophila* model of ALS/FTD
Danielle DiTirro	*C. elegans* Tubby regulates cilia structure and ciliary protein trafficking

The Volen National Center for Complex Systems Poster Session (Cont.)

Presenter	Poster Title
Yasmin Escobedo Lozoya	Developmental plasticity drives E/I imbalance and seizure in an *in vitro* model of Infantile Spasm Epilepsy
Zachary Feiger	Mechanisms for misregulation of membrane traffic and growth factor signaling in animal models of amyotrophic lateral sclerosis
Veronica Flores	Behavioral and neural investigation of experience dependent learning mechanisms in the rat
Maria Genco	The characterization of rhythmic *Drosophila* larval motor neuron activity
Julijana Gjorgjieva	Homeostatic regulation of circuit function
Patricia Goodwin	Regulation of sleep by microRNAs in *Drosophila*
Sara Haddad	Modulators differentially affect robust rhythmic output across temperature
David Hampton	Effects of multiple neuromodulators on *C. borealis* STNS
Josiah Herzog	TDP-43 mediated changes in dendritic morphology via aberrant growth factor signaling
Linnea Herzog	Taste learning in the hippocampus and gustatory cortex
Anne Joseph	Nuclear CaMKIV bidirectionally regulates excitatory homeostatic mechanisms in cortical neurons
Katelyn Kenny	A novel function for the GTPase Rem2 in the nucleus
Zachary Knecht	The molecular basis of hygrosensation in *Drosophila*
Heather Lin	The effects of GRIP1 on synaptic scaling
Chang Liu	Serotonergic activity controls sleep architecture in *Drosophila melanogaster*
Jacqueline McDermott	The role of PlexinBs in Sema4D mediated GABAergic synapse formation
Nate Miska	Visual deprivation-induced synaptic and circuit-level changes in layer 4 of visual cortex

The Volen National Center for Complex Systems Poster Session (Cont.)

Presenter	Poster Title
Narendra Mukherjee	Sensory cortical representation and modulation of decision related motor patterns in the rodent taste system
Lina Ni	Lonotropic receptors mediate cool sensing in *Drosophila*
Sean O'Toole	Post-transcriptional regulation in fast-spiking interneurons
Adriane Otopalik	Modulation of localized transmitter responses in identified neurons of the stomatogastric ganglion
Laura Paige	Age differences in hippocampal activation during false recognition of objects
Emily Parodi	A novel role for Kinesin-1 in microtubule and actin interactions in the developing nervous system.
Sarah Richards	Knockout of Rem2 alters critical period plasticity in mouse visual cortex
Neil Ritter	Modified carbon fiber arrays for dense recording from LGN
Alexander Sutton	Variability and constancy of morphological properties of STG neurons
Rylie Walsh	The retromer complex regulates the abundance of APP-exosomes at the *Drosophila* NMJ
Timothy Wiggin	Describing *Drosophila* sleep patterns using a quantitative behavioral model
Yanxun Yu	Transmembrane guanlylyl cyclases and CaMKI mediate thermosensory signaling and thermal acclimation
Liangfang Zhao	Role of inhibitory circuits in monocular deprivation-induced homeostatic synaptic plasticity
Zhihao Zheng	3D neuron tracing
Mark Zielinski	Disrupting awake sharp-wave ripples increases vicarious trial and error behavior

The M.R. Bauer Foundation Summer Undergraduate Research Fellows

Introduction

The M.R. Bauer Foundation Summer Undergraduate Research Fellows Program completed a third summer in 2016. The M.R. Bauer Foundation generously supported 10 undergraduates' research projects this past summer. Each Brandeis undergraduate was able to perform research in a Volen National Center for Complex Systems laboratory. This opportunity allowed very talented undergraduates to tackle important research questions. More importantly, the M.R. Bauer Foundation Summer Undergraduate Research Fellows Program supported the growth of young, excited but relatively inexperienced budding scientists. As you will read in each fellow's personal statement, the opportunity to pursue research this summer was life-changing. Remi Boros states, "The uninterrupted 10 weeks of support and inspiration were paramount to my development as a scientist, a critical thinker, and a well-rounded individual." Sarah Lipitz and Bethany Rennich both discuss the impact the summer fellowship has had on their long-term career goals, with Sarah writing, "My experiences this summer confirmed my desire to pursue a PhD and a career in research" and Bethany stating, "My work this summer has confirmed what I knew was a passion to pursue neuroscience research as a career, strengthening my desire to attend graduate school." It is due entirely to the generosity of the M.R. Bauer Foundation that these young scientists were able to experience what truly comprises laboratory life and science during summer 2016.

Aaron Ammerman
Oprian Laboratory
Department of Biochemistry
Brandeis University

Spectral Tuning of an Opsin-Guanylyl Cyclase Fusion Protein for Optogenetic Use

Poster Abstract

Rho-GC (bacteriorhodopsin-guanylyl cyclase) is a fusion protein responsible for phototaxis in the fungus *Blastocladiella emersonii.* We are researching Rho-GC for use as an optogenetic tool. We wish to move expression into adult flies to show function as an optogenetic tool. Wild type Rho-GC absorbs green light, which would not penetrate the cuticle of an adult fly (meaning the protein would not be activated). We investigated methods to spectrally tune Rho-GC from a green absorption maximum to red to make the protein sensitive to deeper penetrating light. The binding pocket of *bacteriorhodopsins* comprises three key residues: Lys 216, Asp 85, and Asp 212. Lys 216 binds covalently to retinal by means of a protonated Schiff base linkage, while Asp 85 and Asp 212 serve as counterions to the positively charged nitrogen. Past studies with microbial rhodopsins have found that changing these counterion residues, as well as other residues involved in retinal binding, can result in color shifts. With this in mind, mutations were designed at analog residues in Rho-GC, yielding three spectral tuning mutants: E254D, D380N (both blue shifted mutants), and D380E (a red shifted mutant). Further experiments are necessary to determine new residues to mutate as well as to test the activity of all spectral tuning mutants.

Personal Statement

My time working in the Oprian lab with the funding of the M.R. Bauer Foundation has been absolutely incredible. While this summer of research has helped me develop more lab autonomy by improving my time management and research skills, the biggest impact this summer has had on me was teaching me how to cope with a difficult project. This summer, I found many of my experiments constrained by long reaction times and more unfavorable results than favorable ones. It forced me to face a hard truth: Sometimes you can spend a month on an experiment only to find that it was destined to fail. I began to view my project like a maze: There's only a few correct paths to the center, but a lot of forks in the road leading to false paths with dead ends. This summer had a lot of dead ends. But when I reached a dead end, I did not give up. Instead, I tried to determine why an experiment failed and if there was anything I could do to make the experiment successful. If I could not fix the experiment, then I moved on. I read papers, went to talks, and tried to find a new angle to approach my object. When my efforts gave me a new idea or experiment for my project, I found my PI and coworkers extremely supportive in helping implement my ideas and getting results. I do not know where my project's current path will take me, nor do I know how many more twists and turns are ahead. But I am excited to walk the path, and grateful to the M.R. Bauer Foundation for the opportunity to do so.

Remi Boros
Fraden Laboratory
Department of Physics
Brandeis University

Driving Chaos Off the Grid — Analyzing Networks in Microfluidic Lattices of Chemical Oscillators

Poster Abstract

In nature, living organisms often synchronize to form large, coherent structures. While this synchronous coupling is essential to life as we know it, it remains exceedingly difficult to control. Controlling synchronizations requires the direct manipulation of individual organisms, something that is currently unfeasible on a large scale. To better study large-scale synchronizations, our lab constructs lattices of nanoliter-scale PDMS wells filled with the chemically oscillating Belousov-Zhabotinsky reaction. Depending on their architectures, these lattices can induce different oscillatory patterns between individual wells and their neighbors. With the addition of a photosensitive catalyst, the BZ reaction becomes light sensitive, making it possible to inhibit wells individually when exposed to blue light. Using this technique, one can influence large-scale synchronous behaviors on these lattices with relative ease.

Personal Statement

The lab is a unit made up of smaller bits, each with its passions. The group's character is dictated by everyone's, each capable of change and adaptation. In such a setting, social events and group discussions are just as important as independent accomplishments. One learns to balance work and play, autonomy and communication, for the forward development of the whole.

In retrospect, I think it's fitting that I spent my summer researching network dynamics: I've seen how networks can become interlocked, spastic, difficult to manipulate. With that in mind, I feel lucky to have been given the opportunity to work with such a cohesive group of scientists. Together we solved problems, critiqued one another, socialized. Without direct instruction, they taught me how to effectively describe my thoughts, my data, and my findings. The uninterrupted 10 weeks of support and inspiration were paramount to my development as a scientist, a critical thinker, and a well-rounded individual. Above all, I learned this summer what it means to be part of a productive community of happy, determined individuals and why I want to help such communities thrive.

Emily Cohen
Wingfield Laboratory
Department of Psychology
Brandeis University

Investigating the Effect of Self-Paced Listening on the Relationship Between Hearing Acuity and Speech Recall

Poster Abstract

Increased perceptual effort, due to hearing loss or difficult listening conditions, negatively affects listeners' comprehension and recall performance — even when the words are audible. However, former PhD student Tepring Piquado demonstrated that allowing young adult listeners with mild-to-moderate hearing loss to control the speed of auditory input by self-pacing through passages ameliorates this negative effect of poor hearing acuity on recall. The current study investigates this effect of self-paced listening on poor recall in both young and older adults. Four passages are presented to the young and older adult listeners in self-paced or continuous conditions. In the continuous condition, passages play continuously from beginning to end; in the self-paced condition, passages pause after each sentence and allow the listener to continue at their own pace. Two passages are presented at +10 dB from the listener's speech reception threshold (hard-to-hear) and two at +25 dB (easy-to-hear). After each passage finishes, listeners are prompted to begin their free recall of the passage with as much detail as possible. Each listener's recall is analyzed for amount and degree of detail recalled using propositional analysis (Peelle, et al., 2015). While data are still being analyzed, recall of the self-paced listening condition presented at the easy-to-hear level is expected to be more accurate and more detailed than the continuous listening condition at the hard-to-hear level. These results are expected to have a greater effect for older adults than young adults.

Personal Statement

I have worked at the Memory and Cognition Lab for about a year and a half. I joined during the second semester of my sophomore year, long before officially declaring my psychology major, and it amazes me how much my experiences there have shaped me, both academically and personally. Never having worked in a lab before, I learned everything from organization of data and working with participants to experimental design and excel functions; everything that goes into the setup and execution of an experiment. Having the opportunity to build upon these experiences as a full-time research assistant under the M.R. Bauer Foundation fellowship this summer has provided me with irreplaceable and vital skills. I witnessed all of my hard work from the previous months come to life as an active experiment, and as the attention turned from creating stimuli and organizing trials to running participants and analyzing data, I found myself taking immense pride in this research that I had been a part of since its early stages. I enjoyed running participants, both young and old, seeing them work their way through each trial and condition, and talking to them afterward. I loved hearing their opinions on the experiment, what they found to be helpful, how they perceived all of the stimuli being presented to them. Being a typically more reserved person, having to interact with a complete stranger for an hour and a half — whether giving them instructions, making small talk during breaks, or dealing with any of the inevitable "technical difficulties" that would arise — was initially a challenge for me. As the summer wore on, I became significantly more comfortable with participants, and more confident in myself. I no longer had to check the manual to set up the audiometer or use the script to make sure I touched upon every important point. Interacting with my peers in the lab was another exceptional experience. There was never a shortage of people I could ask if I was confused or unsure about something, or simply if I needed an extra set of eyes. I always felt free to ask questions, and always received an honest and helpful answer, which is truly essential as an undergraduate in a lab. The number of things I have learned this summer is infinite, and I am sure that the experience and confidence I have gained as a result will follow me in all my future endeavors, from this lab and my eventual thesis and beyond.

Mehan Leubner
Lisman Laboratory
Department of Biology
Brandeis University

The Molecular Basis of Memory: Calcium-Calmodulin-Dependent Protein Kinase II (CaMKII) Is Necessary for the Maintenance of Long-Term Potentiation and Behavioral Memory

Poster Abstract

Long-term potentiation (LTP) is a leading hypothesis for the mechanism of memory and involves induction, maintenance, and expression processes. The aim of this research project was to reveal the role of Calcium/Calmodulin-dependent protein kinase II (CaMKII) in the maintenance mechanisms of LTP. This aim was addressed through the use of an erasure test *in vivo* by applying a transient dominant-negative form of CaMKII (K42M) to the CA1 region of the rat hippocampus. K42M was applied after the rat was trained using conditioned place aversion, a hippocampal-dependent form of memory. Memory retention was then tested a week later. The rats injected with K42M entered the shock zone during retention testing more quickly and frequently as compared with the rats injected with GFP, indicating that this form of behavioral memory can be erased by this procedure. Rats from both groups were capable of relearning. This is the first demonstration of the reversal of memory.

Personal Statement

I came to Brandeis for a visit whilst looking at colleges and immediately fell in love with all Brandeis had to offer a student interested in pursuing science. I had always been interested in neuroscience, and came to Brandeis on a quest to learn more about a subject that has the capacity to answer some of life's most befuddling mysteries. I am lucky enough to have had the chance to research one of these great mysteries — how is it possible for the brain to take something as intangible as an experience and maintain it as a memory?

I work in the Lisman Lab part-time year-round studying the molecular basis of memory. This summer, with the generous support of the M.R. Bauer Foundation fellowship, it became possible for me to work full-time and continue making progress toward the discovery of how memories are maintained on a molecular level. The ability to focus on research this summer has further cultivated my interest in neuroscience. I look forward to continuing my work in the Lisman Lab.

Sarah Lipitz
Gutchess Laboratory
Department of Psychology
Brandeis University

Effects of Age on Recruiting the Medial Prefrontal Cortex During Self-Referential Encoding

Poster Abstract

The medial prefrontal cortex (mPFC) is recruited during self-referencing, a cognitive process in which information is related to oneself. In one reported fMRI experiment, younger and older adults were asked to rate adjectives for how well they described themselves; after a 30-minute delay, participants completed a surprise recognition task probing for those adjectives. The results of this study suggest that mPFC recruitment is associated with successful encoding of self-referential memories in both age groups. However, focal differences in neural activation seem to arise between younger and older adults, where younger adults recruit regions involved in emotional processing while older adults recruit regions involved in cognitive control. The present study aims to further understand the effect of age on neural activation during successful self-referential encoding by using more nuanced analyses, such as functional connectivity and multivoxel pattern analysis, or MVPA. Preliminary analyses reveal that both younger and older adults recruit mPFC when encoding adjectives later successfully recognized, yet older adults recruit regions associated with cognitive control such as middle frontal cortex and superior prefrontal cortex. Future connectivity analyses will aim to detect regions functionally linked to mPFC recruitment for younger versus older adults, while MVPA analyses will aim to predict age group and remembered versus forgotten trials based on voxel-specific patterns of neural activation.

Personal Statement

I have been working in the Aging, Culture, and Cognition Lab at Brandeis since my freshman year and spent last summer as a research intern at MGH, but this summer was the first time I had an opportunity to pursue independent research full-time. This opportunity has allowed me to lay the groundwork to spend an entire year asking nuanced questions involving complicated analyses, an opportunity many undergraduates do not receive. Additionally, my experiences this summer confirmed my desire to pursue a PhD and a career in research.

Because of this opportunity, I now realize that I am passionate about both science as well as the community science creates. My lab is a place where I always feel comfortable asking for help, discussing a different opinion, and just enjoying the exciting discoveries made by other researchers in our field. As expected with any independent project, my research this summer has been full of challenges; learning to solve my own problems was such an important step in taking ownership of my research. I am so grateful for the ability to have spent a summer asking questions I never thought I could answer in the company of such bright, inspiring, and supportive researchers.

Elon Mathieson
Katz Laboratory
Department of Psychology
Brandeis University

Tasty Place Cells: Multimodality in the Hippocampus

Poster Abstract

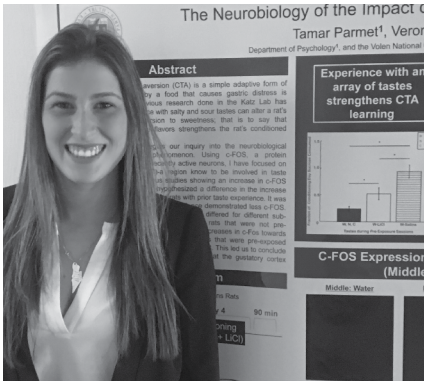
The hippocampus plays a central role in spatial learning and memory. In fact, the CA1 region of the rat hippocampus can be considered a spatial map since it consists of neurons known as place cells that fire in a specific location of the animal's environment. These cells have been known to not only respond to specific locations but other stimuli such as odors. However, there is little research in understanding the role of the hippocampus in relation to taste learning. Prior research has shown that inactivation of the hippocampus interestingly enhances conditioned taste aversion (CTA), a type of associative learning. As a result, the aim of the experiment was to characterize how hippocampal CA1 neurons respond to tastes. Preliminary results suggest that there may be place cells in the hippocampus that also respond to tastes. These "tasty place cells" may play a role in taste learning paradigms such as CTA, as well as offer a relationship between location and taste responses.

Personal Statement

Whether an experience is old or new does not matter but rather the growth that you go through. This summer completes a full year of me being a part of a lab. This opportunity has given me a new perspective on my own growth. In my opinion, the most important characteristic that I have received this summer has been autonomy. I have been given the freedom to explore my ideas as well as offer meaningful discussion. I have grown from simply learning to navigate my environment to being a part of it. What I have gained is an aspect that will continue to last throughout my time at Brandeis and within my lab. I have gained important skills in communicating my ideas, analyzing papers, and critical thinking skills that I would not have gained until later in my career. This opportunity has truly helped my growth as a researcher and as an individual.

Tamar Parmet
Katz Laboratory
Department of Psychology
Brandeis University

The Neurobiology of the Impact of Innocuous Experience on Later Learning



Poster Abstract

Conditioned taste aversion (CTA) is a simple adaptive form of animal learning whereby a food that causes gastric distress is rendered aversive. Previous research done in the Katz Lab has suggested that experience with salty and sour tastes can alter a rat's ability to learn an aversion to sweetness; that is to say that experience with multiple flavors strengthens the rat's conditioned taste aversion to sucrose.

The present study begins our inquiry into the neurobiological underpinnings of this phenomenon. Using c-FOS, a protein byproduct expressed by recently active neurons, I have focused on the gustatory cortex (GC) — a region known to be involved in taste learning. Based on previous studies showing an increase in c-FOS labeling with learning, we hypothesized a difference in the increase in c-FOS expression in GC for rats with prior taste experience. It was found that rats who had prior experience demonstrated less c-FOS. Further investigation showed this result differed for different sub-regions of GC. Specifically, learning in rats that were not pre-exposed to a taste array involved larger increases in c-Fos towards the posterior section of GC, whereas rats that were pre-exposed showed equal amounts of c-FOS across GC. This led us to conclude that taste experience changes the way that the gustatory cortex processes novel tastes.

Personal Statement

The M.R. Bauer Foundation summer undergraduate research fellowship has given me the opportunity to continue my research in the Katz Lab over this past summer. I joined the Katz lab my second semester of freshman year as a naïve freshman with plans to become a doctor. In the Katz Lab, however, I have become aware of the range of career paths that I might want to go down. I made the decision to apply to the M.R. Bauer Foundation summer grant in hopes of better understanding what a career in research would entail. This summer opportunity gave me the unique chance to focus on my research without the pressures and distraction of managing a full course load.

While I have not been able to completely make a decision on whether I will choose medical school or graduate school, this opportunity has given me valuable information that will ensure that my decision is an informed one. I now understand what it means to organize a project, collect and analyze data, and build a scientific poster, all incredibly valuable pieces of information. I am incredibly grateful to have spent my summer working alongside talented and knowledgeable scientists and can only thank the M.R. Bauer Foundation for this incredible opportunity.

Bethany Rennich
Nelson Laboratory
Department of Biology
Brandeis University

Investigating Surf2 in the Context of Conditioned Taste Aversion

Poster Abstract

The ability to form associations between stimuli and consequences in the environment and turn them into long-term memories is an important survival mechanism. Conditioned taste aversion, a robust, single trial learning paradigm, offers a behavioral model to investigate changes in gene expression that contribute to memory formation. Here we study Surf2, a gene downregulated in excitatory cells of the basolateral amygdala following conditioned taste aversion. Cell culture methods were used to overexpress an HA tagged Surf2 construct. Immunohistochemistry and biochemical fractionation were used to analyze the cellular localization of Surf2 protein. The immunohistochemistry results suggest that Surf2 localizes primarily to the nucleus. Several attempts at biochemical fractionation failed to effectively separate the nucleus from the cytoplasm, leaving us unable to confirm the nuclear localization of Surf2. Further study will use *in vivo* viral overexpression to repeat the fractionation and immunohistochemistry experiments. In addition, behavioral experiments will determine the effect Surf2 overexpression has on memory formation.

Personal Statement

This summer, I worked closely with a postdoc mentor and other students in the lab. I applied a range of cell biology techniques to investigate how neurons regulate gene expression to effect changes in the network and produce long-term memory. Working on this project gave me the opportunity to learn and develop many new skills and techniques such as cell culture, virus production, western blot, and plasmid cloning. In addition, the academic side of science was emphasized by a weekly undergraduate journal club set up by our PI. Together, we learned how to read scientific papers, explored new ideas, and practiced effectively communicating scientific ideas. This experience has given me the opportunity to deepen my understanding of science and enrich what I have learned in the classroom. Furthermore, my work this summer has confirmed what I knew was a passion to pursue neuroscience research as a career, strengthening my desire to attend graduate school.

Ayantu Temesgen
Kern Laboratory
Department of Biochemistry
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A Memo From Millennial Kinases to the Lost Generation: "We Are Not So Lazy After All!"

Poster Abstract

Src and Abl are two non-receptor Tyrosine kinases that have similar structures but different regulatory mechanisms. Kinases are enzymes that phosphorylate Ser, Thr and Tyr residues by transferring a phosphate group from ATP. Phosphorylation often functions to turn a protein "on" or "off," and plays a central role in cellular communication. Uncontrolled kinase activity leads to uncontrolled cell growth and ultimately cancer making kinases important drug targets.

In order to gain insight into the evolution of kinase regulation, we resurrected common ancestors of Src and Abl, and then Src, Abl and the Tec and Fer families. We manipulated various regulators, such as myristoylation for Abl and tail phosphorylation for Src, to get quantitative information on the distinct regulatory modes of the modern enzymes. We then used the same methods on the ancestors in order to understand the evolution of regulation.

Personal Statement

Starting out in the Kern lab, I was like most undergrads; I was nervous, I had little to no clue what was going on during the first few lab meetings, and I dedicated my entire daytime to learning new lab skills and perfecting them. Fortunately, I had a mentor who was very understanding and willing to help me learn. Once I felt comfortable with the basic skills, I then focused on getting to know "my" proteins on a deeper level, as this is vital for understanding the question we are trying to answer. I slowly transitioned from being excited about or disappointed by the simplest of experiments — also known as being naïve— to being accustomed to the unexpected twists I encountered during most experiments — that is, improving my problem-solving skills. As for the science I partake in in lab, it involves two human tyrosine kinases: Src and Abl. Kinases take part in myriad cellular activities and so, are tightly regulated in the cell, which means that uncontrolled kinase activity can lead to cancer. In lab, we manipulate the various allosteric regulators to gain insight into the differential regulatory mechanisms of Src and Abl. We also use resurrected ancestors of Src and Abl to study the evolution of kinase regulation.

My experience in lab has been great so far and the Bauer Undergraduate Summer Research Fellowship has contributed profoundly to my experiences this summer. The Bauer Fellowship has allowed me advance my current project without the distractions of having to take classes or work other jobs. As a rising senior, being a Bauer Fellow also meant having the opportunity to start thinking about and gathering data for my thesis. Because one of the requirements for the Bauer Fellowship was to give back to the community in some way, I was also able to get to know some of the other fellows as we plan for the coming academic year. Overall, this summer has truly been a valuable experience and I am grateful to have had the support of the Bauer Fellowship.

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Rhythmic Release of an Antidepressant by an Enzyme System

Poster Abstract

Sarcosine is a derivative of glycine, and has previously shown to help patients with obsessive-compulsive disorder (OCD). The antidepressant activity is a result of enhancing the activity of NMDA receptors in the brain, which help the brain adapt and involve in memory. Since sarcosine is a product of enzymatic action of creatinase on creatine, we use this enzymatic system as the source of sarcosine. Here, we aim to deliver sarcosine in a self-sustained and oscillatory manner; for this purpose, we couple a pH oscillator with the enzymatic reaction mentioned above. Our initial simulations show the existence of bistability, which depends on the concentration of creatine.

Personal Statement

The M.R. Bauer Foundation Summer Undergraduate Research Fellowship offers a great research experience to me. At the Nonlinear Dynamics group at Brandeis, I am interested in finding a mechanism to produce and deliver sarcosine, an antidepressant, with self-sustained oscillatory manner. The oscillatory mechanism consists of creatine-creatinase and urea-urease reactions, as well as a coupled pH oscillator. During the last 10 weeks, I have been working on finding the physical-chemical conditions required for the coupled enzymatic reaction systems to produce sarcosine, and on solving the differential equations of our model numerically using an in-house MATLAB script. At the end of the summer, I presented my poster named “Rhythmic Release of an Antidepressant by an Enzyme System” to more than 100 Brandeis faculty and students.

The M.R. Bauer Foundation fellowship is important to me not only because it generously offered me a stipend but also because of the invaluable experience and knowledge I’ve gained through the whole process. I am also glad that I can give back to Brandeis community and promote science as one of the Bauer fellows. By investigating on this creative task, and with help from my group, and with the support of Bauer Fellowship, I believe I am shaped and prepared for future graduate study.

Acknowledgments

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

We especially acknowledge Kim MacKenzie, a past neuroscience PhD graduate, 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.

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