
Brandeis University

Benjamin and Mae Volen National
Center for Complex Systems

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**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, Distinguished Lecturer Series, Annual Scientific Retreat, and Summer Science Research Fellowship 2014-2015 Summary

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The 2014-2015 M.R. Bauer Foundation Colloquium Series, Distinguished Lecturer Series, Annual Scientific Retreat, and Summer Science Research Fellowship

Introduction

The Volen National Center for Complex Systems supports the work of scientists, undergraduates, graduate students, and established researchers alike. All of us, together, have embarked on a new year of research that advances the Volen Center's place in the field of neuroscience.

This work is occurring in challenging times. Government investment in science is still low, and public discourse can be disappointing. Our research is invigorating, and we work hard to keep the enterprise afloat.

The Colloquium Series and Distinguished Guest Lecturer Series provide safe harbor from turbulent seas. These events guide and inspire us. After 18 years, I know that our gatherings are immensely valuable and deeply influential, especially to the undergraduate and graduate trainees who are the future of neuroscience.

Alongside its impressive science, the legacy of the Volen Center lies in promoting a collaborative ethos. The M.R. Bauer Foundation enables us to share our work, practices, and ambitions, and we are immensely grateful for its unwavering belief in the power of science to change minds and the world in positive ways.

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

As the astrophysicist and science commenter Neil Degrasse Tyson remarked, “Everything we do, every thought we’ve ever had, is produced by the human brain. But exactly how it operates remains one of the biggest unsolved mysteries, and it seems the more we probe its secrets, the more surprises we find.” How can these mysteries be solved? What are the best approaches for this undertaking? While understanding the properties and activity of single neurons is vitally important, it is understanding how these neurons work together that will truly provide an understanding of the brain.

Neurons form networks — connections between multiple neurons and between multiple areas of the brain — in order to generate complex behaviors. For example, as the work of one speaker explores, detection of taste can lead to particular motor behaviors, through a network of neurons between two areas of the brain. Alterations in these networks, due to neurological damage or disorders, can disrupt these behaviors.

The 2014-2015 M.R. Bauer Colloquium Series focused on methods of exploring neural networks among multiple sensory areas. Ten distinguished scientists discussed insights and methods of exploring the functions of neural networks, using organisms ranging from the simpler nervous systems of the worm *C. elegans* and the fruit fly, to transgenic mice, to humans and artificial neural networks. Each speaker has presented a summary of his or her work, which is preceded by a brief introduction, set in italics, explaining the research in the more general framework of the effect on neural networks and behavior.

Anatol Kreitzer, PhD

Department of Physiology and Gladstone Institute of Neurological Disease
University of California, San Francisco
(October 1, 2014)

Basal Ganglia Circuit Mechanisms Underlying Motor Function & Dysfunction

What neuronal networks are responsible for controlling the movements we make? How does the brain progress from the decision to make a movement to the action of making the movement? The basal ganglia are the structures necessary for this function, and these neuronal networks are affected in disorders such as Parkinson's and Huntington's disease. In his talk, Dr. Kreitzer presented his work on how the cells of the basal ganglia and cells in the brain stem form networks critical for locomotion. Using multiple techniques, including recording from single cells and genetically modified animal models, Dr. Kreitzer is investigating how the neurons of the basal ganglia control motor movements.

a motor program through cell-type-specific regulation of neurons linked to specific actions.

Previous work has demonstrated that subsets of neurons in the MLR are correlated with locomotion, and a recent optogenetic study indicates that MLR glutamate neurons are sufficient to induce locomotion. However, less is known about the activity of identified MLR glutamate neurons in vivo, and whether their activity is actually necessary for locomotion. Moreover, the function of the cholinergic and GABAergic populations is not clear, and debate still remains as to whether some or all of the effects seen during electrical stimulation can be attributed to the glutamatergic or cholinergic population.

The basal ganglia (BG) are critical for adaptive motor control, but the circuit principles underlying their pathway-specific modulation of target regions are not well understood. We dissected the mechanisms underlying BG direct- and indirect-pathway-mediated control of the mesencephalic locomotor region (MLR), a brainstem target of BG that is critical for locomotion. We optogenetically deconstructed the locomotor function of the three neurochemically distinct cell types within the MLR.

We found that the glutamatergic subpopulation encodes locomotor state and speed, is necessary and sufficient for locomotion, and is selectively innervated by BG. We further showed activation and suppression, respectively, of MLR glutamatergic neurons by direct and indirect pathways, which is required for bidirectional control of locomotion by BG circuits. These findings provide a fundamental understanding of how the BG can initiate or suppress

To investigate the locomotor function of MLR cell types and their control by BG circuitry, we combined cell-type-specific optogenetic manipulations, in vivo single-unit recordings from identified cells, viral-based circuit mapping, and high-resolution behavioral assays to explore how signals from the BG are transduced into locomotion through the MLR. Our results highlight the functional differences among cell types in the MLR and the remarkable specificity of BG-brainstem projections. In addition to defining the pathway through which the BG regulate locomotion, these results provide a more general framework for how the BG can initiate or suppress action by specific modulation of neuronal subtypes associated with a motor program.

Kathleen Cullen, PhD

Department of Physiology
McGill University
(October 15, 2014)

Neural Representations of Natural Self Motion: Implications for Perception and Action

How do we control our motions and orient our bodies in space? The vestibular system is critical to the control of balance and movement. Most people do not give much thought to their vestibular system until it malfunctions. Problems with the vestibular system can lead to dizziness and a loss of balance – both of which can lead to falls and broken bones. The Cullen laboratory examines how the brain processes information from the vestibular system and uses that information to predict the outcomes of self-motion. By measuring responses at the level of single neurons, Dr. Cullen is learning how patterns of neuronal firing change when a movement is self-generated compared to those externally directed. Dr. Cullen's research will also have an impact on treatments for those with a loss of vestibular function.

To advance our understanding of brain disorders, it is necessary to identify the underlying neural circuits and determine how abnormalities in these circuits produce cognitive and behavioral symptoms. The overarching focus of my research program is to develop an understanding of neural circuits underlying vestibular disease, with an emphasis on translational approaches for restoring sensory function. The loss of vestibular function due to aging, injury, or disease produces dizziness, imbalance, and an increased risk of falls — all symptoms that profoundly impair quality of life. Thus, vestibular disorders impose a substantial burden on the economy in the form of increased medical costs, work-related absenteeism, and reduced productivity.

Recent research from my laboratory has advanced our fundamental knowledge about the neural circuits responsible for normal vestibular function and reveal how these circuits are altered by disease to

develop innovative treatment options. The research program is aimed at addressing two central challenges.

The first is to understand how the brain processes vestibular information to ensure accurate perception and behavior in everyday life. I described recent progress made toward understanding the nature of the neural code that used to represent vestibular sensory input. Using computational modeling and experimental approaches, my group has shown through its work how heterogeneities in the intrinsic neural variability of early vestibular pathways determine the nature of the neural code (i.e., rate versus temporal coding). In addition, work from my laboratory has revealed how we distinguish between our own self-generated movements and those of the external world. While vestibular brainstem and cerebellar neurons show robust responses to externally applied motion, these responses are canceled when motion is self-generated. By completing trial-by-trial analysis of voluntary head movements, my laboratory has further shown that the brain performs this elegant neural computation by computing an internal expectation of the expected sensory consequences of active self-motion.

The second challenge of my lab's research program is to understand the neurophysiology of vestibular/balance disorders and develop new treatment approaches. Specifically, by measuring activity in these circuits after vestibular loss at the level of single neurons, their recent findings establish how changes in coding, including altered multimodal integration, impact perception and behavior. In ongoing experiments, my lab is now using this information to drive novel rehabilitation strategies to treat patients in part through development of implantable vestibular prostheses.

Kristin Scott, PhD

Division of Neurobiology and Helen Wills Neuroscience Institute
University of California, Berkeley
(October 22, 2014)

Taste Processing in *Drosophila*

*The experience of taste only begins on the tongue. Messages sent from the taste buds to the brain determine the behavior — whether a food is accepted or rejected. This process is further complicated by the fact that our behavior toward a certain taste can change based on how hungry we are and what experience we have had with the taste in the past (e.g. something that has made us sick in the past is less likely to be found palatable). Dr. Scott discussed her work on taste processing in *Drosophila*. Despite the simplified nervous system of fruit flies, they respond to many similar tastes as humans. Dr. Scott has determined that the Gustatory Receptor gene family plays an important role in detecting taste in the fruit fly. Dr. Scott is also examining how detection of taste can, through neuronal networks, drive motor behaviors.*

The ability to identify food that is nutrient-rich and avoid toxic substances is essential for an animal's survival. Although olfaction and vision contribute to food detection, the gustatory system acts as a final checkpoint control for food acceptance or rejection. The fruit fly, *Drosophila melanogaster*, tastes many of the same stimuli as mammals and provides an excellent model system for comparative studies of taste detection. The relative simplicity of the fly brain and behaviors, along with the molecular genetics and functional approaches available in *Drosophila*, allow the examination of gustatory neural circuits from sensory input to motor output. These studies provide insight into how taste compounds are detected and processed by the brain.

A major interest of the laboratory has been to identify and characterize the receptors that detect different taste compounds in *Drosophila*. Although insects show behavioral responses to taste compounds that are similar to mammals, the number and types of taste receptor molecules was unknown. Our work characterized the role of the Gustatory Receptor gene family in the detection of sweet and bitter compounds and the role of a class of ion channels in water and pheromone detection, and it identified a new taste modality, the taste of carbon dioxide. These studies uncovered molecular mechanisms of taste detection in insects and revealed that the principle of modality-selective cells is a conserved coding strategy.

Detection of taste compounds drives innate motor programs for feeding in *Drosophila*, making it an excellent model to study sensorimotor transformations. A major current research interest is to elucidate neural circuitry for taste behaviors to examine sensory propagation and behavioral decisions. In addition, responses to taste compounds are plastic and modified by intrinsic and extrinsic cues, such as hunger, satiety, and experience.

Our studies of plasticity have described neural mechanisms that modulate circuits and behavior, and resolved how single modulatory neurons can have widespread consequences for behavior.

Kang Shen, PhD

Department of Biology
Howard Hughes Medical Institute
Stanford University
(November 5, 2014)

Molecular Mechanisms of Dendrite Morphogenesis in *C. Elegans*

Neuronal circuits and networks are formed when neurons form synaptic connections: a point of communication from one neuron to another. The synapse is this point, the spot where the signals from one neuron reaches the dendrite of the next. The growth and branching of dendrites, like the branches of a tree, affect how connections and networks eventually form. Dr. Shen has identified a receptor, DMA-1, that helps to regulate the growth and branching of dendrites. Too much or too little DMA-1 can halt dendritic growth or alter development, eventually affecting the formation of networks of neurons.

Extracellular adhesion molecules and their neuronal receptors guide the growth and branching of axons and dendrites. Growth cones are attracted to intermediate targets, but they must switch their response upon arrival so that they can move away and complete the next stage of growth. Here, we show that KPC-1, a *C. elegans* Furin

homolog, regulates the level of the branching receptor DMA-1 on dendrites by targeting it to late endosomes.

In a *kpc-1* mutant, the level of DMA-1 is abnormally high on dendrites, resulting in trapping of dendrites at locations where a high level of the cognate ligand, the adhesion molecule SAX-7/L1, is present. The misregulation of DMA-1 also causes dendritic self-avoidance defects. Thus, precise regulation of guidance receptors creates flexibility of responses to guidance signals and is critical for neuronal morphogenesis.

David D. Ginty, PhD

Department of Neurobiology
Howard Hughes Medical Institute
Harvard Medical School
(January 21, 2015)

The Functional Organization of Neurons That Underlie the Sense of Touch

A gentle touch to the arm, the feeling of a hand on the shoulder — how do we recognize these sensations? Dr. Ginty's work focuses on a type of sensor, the low-threshold mechanoreceptors, and their role in the detection of touch. Using a mouse model, Dr. Ginty has determined that these mechanoreceptors are directly connected, in an organized fashion, to the spinal cord. Dr. Ginty's research is currently examining the hypothesis that different subtypes of mechanoreceptors are part of a network of spinal cord neurons and interneurons that project processed touch information directly to the brain.

The somatosensory system endows us with a remarkable capacity for object recognition, texture discrimination, sensory-motor feedback, and social exchange. Innocuous touch of the skin is detected by a large group of physiologically distinct low-threshold mechanoreceptors (LTMRs) whose cell bodies are located in dorsal root ganglia and cranial ganglia.

In this lecture, I describe our recent advances in genetic labeling of LTMR subtypes and our findings regarding the function, development and organization of LTMRs circuits that underlie the sense of touch. My colleagues and I have generated a mouse LTMR molecular-genetic toolbox that enables interrogation of the physiology, morphology, function, and development of each LTMR subtype. Using these genetic tools and anatomical and physiological approaches, we have defined developmental, morphological and functional properties of LTMRs. We found that neurons that form circumferential endings associated with hair follicles respond to gentle stroking of the skin. We also observed

that LTMR subtypes whose peripheral projections innervate the same small region of skin exhibit central projections that terminate within narrow, three-dimensional columns of the spinal cord dorsal horn. These spinal cord LTMR columns represent units of functional organization that receive and process LTMR subtype activity ensembles emanating from the skin.

We posit that spinal cord interneurons directly receive and process LTMR activities, whereas spinal cord projection neurons carry processed touch information from spinal cord LTMR columns to the brain. To test these ideas and to gain insight into touch information processing in the spinal cord, we recently generated an array of spinal cord dorsal horn neuron subtype-specific molecular genetic tools that enable functional characterization of spinal cord dorsal horn neuronal populations. Mouse lines that enable analysis of 11 distinct spinal cord interneuron subtypes are being used to elucidate the development, physiological properties, morphologies, synaptic connectivity patterns, and functions of spinal cord interneuron subtypes. Thus, at least 11 distinct neuronal types in the spinal cord dorsal horn receive and process LTMR inputs. The mechanisms of development of LTMR subtypes, and the functional organization of LTMR circuits within the spinal cord dorsal horn that underlie the perception of touch are the focus of current research.

Diane Lipscombe, PhD

Department of Neuroscience and Brown Institute for Brain Science (BIBS)
Brown University
(February 4, 2015)

Neuronal Calcium Channel Cell Specific Splicing: Patterns & Properties

Neurons fire in response to changes in the levels of ions such as sodium, potassium, and calcium. The ions enter the cells through channels that open and close in response to changes in the neuron, for instance, changes in voltage across the cell's membrane. Dysfunction in any of these channels can lead to problems, including neurologic or psychiatric disorders. Dr. Lipscombe explores the genesis of differences in calcium channels, by pinpointing how these channels are created at the genetic level — at the level of an early process known as alternative RNA splicing. Alternative splicing can lead to variations in calcium channels that could affect both the behavior of an organism and its response to different substances and medications.

Voltage-gated calcium channels generate rapid, transient intracellular calcium signals in response to membrane depolarization. Neuronal CaV channels regulate a range of cellular functions and are implicated in a variety of neurological and psychiatric diseases. Each of the 10 mammalian *Cacna1* genes that encode the main subunits of CaV channels has the potential to generate tens to thousands of CaV channels by alternative pre-mRNA splicing. Alternative pre-mRNA splicing may enrich the pool of CaV channel structures and functions used by cells. The coordinated expression and activity of available nuclear splicing factors determines the composition of the pool of CaV channel isoforms in a given cell type. The activity of splicing factors are in turn regulated by other molecules that regulate various cellular features, including cell-type, activity, metabolic states, developmental state, and other factors.

We study the cellular and behavioral consequences of individual CaV splice isoforms and the cell-specific splicing factors that control exon selection. Altered patterns of alternative splicing of CaV pre-mRNAs can impact the behavior of an organism in subtle but measurable ways, with the potential in humans to influence drug efficacy and disease severity. The composition of the pool of CaV mRNA splice isoforms varies with cell-type, stage of development, and possibly neuronal activity. Thus, anticipated functional differences among splice isoforms within a given CaV family are either individually or collectively contributing to neuronal processes.

Alternatively spliced exons are present in >95% of multi-exon genes suggesting that cellular control over exon selection must play a critical role in normal development and cell function. But, the cellular and behavioral consequences of only a few CaV splice isoforms are known. I discuss our approaches to determine them. I show that at least for certain sites of alternative splicing in *Cacna1* genes, exon choice and the resultant changes in CaV channel activity affect behavior. Specifically, the enrichment of an alternatively spliced exon of *Cacna1b* in capsaicin-responsive nociceptors of dorsal root ganglia impacts the cellular and the analgesic actions of morphine in vivo.

BJ Casey, PhD

Departments of Psychiatry and Neuroscience
Sackler Institute for Developmental Psychobiology
Weill Medical College of Cornell University
(February 11, 2015)

Self-Control and the Teen Brain: Arrested Development or Adaptive Evolution

How often do we hear about a teenager making a very bad choice? How often do we hear about teenagers experimenting with drugs, binge-drinking alcohol, or starting fights and acting out? How often are these teenagers labeled as deviant, or lacking in some essential brain function causing them to act abnormally? As Dr. Casey explains, bad choices and a lack of self-control are perfectly normal aspects of teenage behavior. Dr. Casey's research has shown that the adolescent brain is still wiring and fine-tuning connections, building the neural networks responsible for emotion and self-control. The experiences of the teenage years, including experimentation and the test of boundaries, can lead to the healthy development and brain functioning of the adult.

Over the past decade, the teen brain has received significant attention from the media, due in part to the many seeming contradictions in teen behavior and in part to developments in brain imaging that provide the opportunity to look under the hood of the teen brain (Casey, 2013). This developmental period is one when an individual is probably stronger, of higher reasoning capacity, and more resistant to disease than ever before, yet mortality rates increase by 200 percent. These untimely deaths are not due to disease but to preventable deaths associated with adolescents putting themselves in harm's way (e.g., accidental fatalities, suicide) with sensation seeking at an all-time high (Steinberg et al. 2008) and anxiety and mood disorders peaking (Kessler et al. 2005, Merikangas et al. 2010).

So what brain changes take place during adolescence that may explain these seeming inconsistencies in behavior? Too often in describing the adolescent brain, we suggest it has no brakes or steering wheel

(Bell & McBride 2010), as if it is defective in some way. However, we don't characterize other formative years of development as defective (Steinberg 2012). When a newborn is unable to talk or walk we do not refer to this inability as a deficit but rather as normal development. Yet the adolescent who makes a bad choice in the heat of the moment among peers is described as having no frontal lobe or as being deviant in some way. Rather than depicting the teen brain and teen behavior as defective, we portray a brain that is sculpted by evolutionarily based biological constraints and experiences as it adapts to the unique intellectual, physical, sexual, and social challenges of adolescence and successfully transitions from relative dependence to independence from the parent.

We present evidence that these alarming health statistics are in part due to diminished self-control — the ability to inhibit inappropriate desires, emotions, and actions in favor of appropriate ones (Casey, 2015). Changes in self-control during adolescence parallel a series of developmental cascades in the wiring and fine-tuning of connections within complex subcortical and cortical prefrontal and limbic circuitries. These adolescent-specific changes reflect both evolutionarily based biological constraints and unique experiences of this period. Having sufficient time and space to freely explore and experiment may enhance the formation of the adolescent's self-identity (Erikson 1968) and lead to healthy development into a socially functioning adult.

The M.R. Bauer Foundation Distinguished Guest Lecturer Series

Introduction

Every year, the M.R. Bauer Distinguished Guest Lecturer program brings to campus two well-known and visible scientists 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 René Hen from Columbia University and Eric Herzog from Washington University in St. Louis.

René Hen, PhD

New York State Psychiatric Institute
The Kavli Institute for Brain Science
Columbia University
(Week of October 29, 2014)

Role of the Hippocampus in Anxiety and Depression

A traumatic experience can have lasting consequences. For those with post-traumatic stress disorder, a seemingly innocent stimulus, such as a sound or smell, can lead to feelings of intense anxiety or panic. One explanation for this rests in a malfunction in the hippocampus, an area of the brain involved in memory formation. When a new memory is formed, it goes through a process of pattern separation, which helps to distinguish that memory from memories of similar experiences. If pattern separation is not complete, the overlapping memories could make it difficult to distinguish safe memories from those associated with danger, leading to the inappropriate responses to safe stimuli seen in PTSD. In his talk, Dr. Hen proposed that an impairment in pattern separation could be due to a malfunction in the creation of new hippocampal neurons in the dentate gyrus. His research has shown that stimulating the creation of new neurons in the dentate gyrus aided in pattern separation and decreased anxiety in a mouse model. He proposed that this could be a potential target for PTSD treatment.

Almost one-third of adult Americans will have an anxiety disorder in their lifetime, with enormous personal, societal, and financial costs. Among the most disabling of these disorders are post-traumatic stress disorder (PTSD), obsessive compulsive disorder (OCD), social anxiety disorder, generalized anxiety disorder and panic disorder. Although there are evidence-based treatments for these disorders — usually selective

serotonin reuptake inhibitors (SSRIs, e.g. fluoxetine) or cognitive-behavioral therapy — as many as 50 percent of patients do not respond, and even those who do respond often continue to have clinically significant residual symptoms and impairment. Therefore, there is a considerable need for new therapies for these disorders, yet well-validated translational targets for such therapies remain unidentified, as is true for most psychiatric disorders. This presentation will investigate a novel treatment strategy for patients with pathological anxiety: stimulating hippocampal stem cells to produce new neurons that will enhance the neural process of pattern separation.

The mature mammalian brain contains two regions where stem cells continuously generate new neurons, a process termed adult neurogenesis; the subventricular zone contributes new neurons to the olfactory bulb, and the subgranular zone of the dentate gyrus (DG) produces new excitatory cells in the hippocampus. The DG and neurogenesis within the DG appear to play a key role in pattern separation during hippocampal memory formation. Pattern separation is thought to function by transforming similar sensory inputs into discrete, non-overlapping representations to disambiguate memories of similar experiences. In healthy organisms, generating and maintaining distinct memories of similar experiences are important for many learning processes. Of relevance to this presentation, this ability allows an organism to distinguish dangerous situations from safe situations. Impaired pattern separation may lead to excessive generalization of previously encountered aversive events to new “innocuous” experiences, a feature often found in anxiety disorders. For example, for someone who developed

PTSD as a result of 9/11, the sight of a plane flying over New York City may trigger a flashback. Patients who have experienced a panic attack in one setting (e.g., an elevator at work) often describe generalization of fear to similar settings (e.g., all elevators, then all closed spaces). This excessive generalization of fear leads patients to avoid people, places, and things, which in turn leads to functional impairment.

We propose that the excessive generalization seen in patients with pathological anxiety is due to impaired hippocampal functioning and specifically a deficit in the neural process of pattern separation, which relies upon the dentate gyrus and is sensitive to neurogenesis. Our preclinical findings indicate that stimulating DG neurogenesis improves pattern separation and also reduces anxiety behaviors in mice. As a result, we hypothesize that pharmacological or environmental manipulations aimed at stimulating neurogenesis will be beneficial for the treatment of anxiety disorders.

Erik Herzog, PhD

Department of Biology
Washington University in St. Louis
(Week of March 7, 2015)

For Whom the Bells Toll: Networked Circadian Clocks in the Brain

What is it about jet lag that makes us feel like zombies? Why does it take days to recover from a week on the night shift? Our internal clock, our circadian rhythms, keep our bodies entrained to a light/dark cycle that can be difficult to disrupt. But this cycle can be disrupted, and Dr. Herzog's work explores how the activity of specific neurons can synchronize the body with the changing seasons and periods of light and dark. His research shows that a certain chemical messenger in the brain, and the neurons it activates, can change the rhythm of firing in multiple neurons within the network. His work demonstrates how altering the activity of part of a network can affect the whole, and adds to our understanding of how networks can adapt.

In my first seminar, titled "Maps and modules in the atomic circadian clock," I aimed to discuss evidence that many mammalian cell types have the capacity to generate sloppy daily rhythms in gene expression. When these cells communicate with each other, their rhythms increase in amplitude and become precise from day to day. I summarized data from my lab and the field showing that the cells of a master circadian pacemaker in the brain, the suprachiasmatic nucleus (SCN), use a neuropeptide (vasoactive intestinal polypeptide, or VIP) to synchronize to each other and a neurotransmitter (GABA) to balance the synchrony among SCN cells. I related these findings to how the system normally synchronizes (entrains) to the local light-dark cycle and adapts to seasons. I presented unpublished data showing, for example, that optogenetic activation of VIP neurons produces a phenomenon we call "phase tumbling." We find that when VIP neurons of the SCN are driven to fire in specific patterns,

the rhythms of cells within the SCN assume more random phase relationships and more rapidly adjust to changes in the light-dark cycle. These results provide a way to understand the limits of normal entrainment and a potential therapy for jetlag and shift-work disorders.

In my second seminar, titled "For whom the bells toll: Networked circadian clocks in the brain," I discussed evidence that tissues within mammals act as coupled circadian oscillators to regulate daily rhythms in physiology and behavior. I used the olfactory system as an example of a network of circadian pacemakers that drive daily rhythms in performance. I showed that mice can detect odors (e.g. vanilla) about six times better at night than during the day. Consistent with this, the olfactory epithelia and olfactory bulbs generated daily rhythms in gene expression, firing rate and neuropeptide release in vivo and in vitro. The daily rhythm in olfactory performance does not require the SCN but does depend on the canonical transcription-translation negative feedback loop functions so that loss of key clock genes, Period 1 and 2, results in mice that are constitutively super smellers, and mice lacking Bmal1 are chronically insensitive to odors. I showed unpublished data including evidence that, like the SCN, the olfactory clock system depends on the neuropeptide VIP for cell-cell synchrony and coherent daily rhythms in performance. I concluded with new data showing that glia (specifically astrocytes) are also circadian

pacemakers, which provided me an opportunity to discuss chronotherapy.

Chronotherapy seeks to treat disorders with drugs at the time of day when they are most effective and with the least amount of side effects. I shared unpublished data where we treat glioblastoma medullaforme cells at the time of their daily peak in Bmal1 to maximize the effect of a standard chemotherapeutic on brain cancer outcomes.

The Volen National Center for Complex Systems Scientific Retreat 2014

Introduction

The Volen National Center for Complex Systems held its annual scientific retreat from October 17-18, 2014. The work of the keynote speaker, Richard Granger of Dartmouth College, set the theme for the retreat: “Complex models and complex behaviors.” Faculty, postdoctoral fellows, and students alike traveled off campus to the Provincetown Inn in Provincetown, Mass. Being away from campus allows the scientists to interact apart from their familiar surroundings and fosters connections and communication that lead to interdisciplinary and innovative collaborations — collaborations that are far less likely to be initiated during the normal bustle of day-to-day life in the laboratory.

In addition to the keynote speaker, we had four Brandeis-affiliated presentations. Two neuroscience postdoctoral fellows, Julijana Gjorgieva and Marc Nahmani, presented in the early morning, followed by presentations by the two most recently hired neuroscience faculty members, Jennifer Gutsell and Shantanu Jahdav. As the summaries that follow will make clear, the 2014 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 17, 2014

2:00 p.m.

Arrival

4:00 p.m.

Keynote Speaker

Richard Granger, Dartmouth University

"From Percept to Concept: Proposed
Brain Circuit Computation"

5:00 p.m.

Dinner

6:30 p.m.

Poster Session

8:30 p.m.

Social Mixer

October 18, 2014

9:00 a.m.

Julijana Gjorgjieva, Marder Lab

"Theoretical principles underlying
neural circuit development and
sensory pathways diversification"

9:45 a.m.

Marc Nahmani, Turrigiano Lab

"Structure and function of an inhibitory
circuit regulating critical period
plasticity"

10:30 a.m.

Jennifer Gutsell, Department of
Psychology

"Resonating with allies and
competitors: A motivational approach
to how the brain processes other's
inner states"

11:15 a.m.

Shantanu Jahdavi, Department of
Psychology

"Neural activity patterns required for
learning and memory-guided behavior"

Noon

Lunch

2:00 p.m.

Departure

Richard Granger, PhD

Department of Psychological and Brain Sciences and Thayer School of Engineering
Dartmouth College
(October 17, 2014)

From Percept to Concept: Proposed Brain Circuit Computation

The human brain is an engineering marvel. The quest for building an artificial brain, and artificial intelligence, has been stymied by the fact that some tasks that seem to be very easy and automatic for the human brain (such as language learning) are much more difficult for an artificial brain. How would an artificial brain tell the story of what is happening in a video or picture, for example? In his talk, Dr. Granger discussed the development of algorithms for use in artificial brain networks through actual data from human research. His work focuses on creating algorithms that approach different human brain functions, such as attention, language, and semantics learning, in hopes that these can help in understanding how similar processes are constructed in humans.

Easy tasks for humans are often the most difficult for artificial systems, and vice versa. Many cognitive tasks are ill-specified, and the only reason we know that current impressive engineering systems for vision and language can be outperformed is that biological systems outperform them. Development of algorithms derived from brain circuits may thus be a highly pragmatic path to engineering designs of substantially more intelligent systems, as well as leading to a scientific understanding of how cognition arises from brains. Current artificial neural network/"deep learning" models represent a surprisingly modest subset of brainlike algorithms. This perhaps accounts for the current wide gap between the capabilities of even the most advanced extant artificial systems and human capabilities (e.g. rapid learning from few instances,

learning by being taught, attentional mechanisms, navigation, structure, temporal sequences, and semantic language meaning). This gap is large in most realms other than statistical "big data" analysis. The assortment of architectural layouts across brain structures, although richly diverse, is nonetheless sharply constrained — by allometry, repeated design, component precision, Amdahl fractions of specific algorithms (see Granger 2011; 2015) — giving rise to a circumscribed "instruction set" of derived elemental operations from which all complex perceptual and cognitive abilities presumably may be composed. Derived brain circuit algorithms include many that are not typically thought of as primitive: sequence completion, hierarchical clustering, retrieval trees, hash coding, and compression are all (unexpectedly) directly derived from the structure and operation of particular circuits (see Rodriguez et al., 2004; Granger 2006).

A number of software and hardware implementations of these brain circuit systems have been analyzed for computational costs and efficacy and carefully tested against standard approaches on known data sets (images, videos, speech, robotics, navigation), with published positive results and field tests (Moorkanikara et al., 2009; Chandrashekar et al., 2012; 2013; Bowen et al., 2015; Nunes et al., 2015). If the derived instructions

constitute the basic operations from which complex mental abilities are constructed, it may be possible to establish a unified formalism for description of human faculties from perception and learning to reasoning and language; this is an ongoing study topic (Rodriguez & Granger 2015). Also of interest are tests of the limits of these capabilities. Initial results unexpectedly suggest that these brain mechanisms are equivalent to nested-stack pushdown grammars, long noted as the estimated size of human natural languages but far short of Turing-complete, and even short of fully context-sensitive grammars. These families of nested-stack grammars are nonetheless very computationally powerful; both their capabilities and their limits may be of scientific and engineering interest (Rodriguez and Granger, 2015).

Julijana Gjorgjieva, PhD

Department of Biology
Brandeis University

Theoretical Principles Underlying Sensory Pathways Diversification

The human brain consists of a dizzying number of different types of cells. Computers store and process information with simple switches — why do we need diversity in neuronal populations? Dr. Gjorgjieva's research uses computational methods to assess how diversity in the types of signaling neurons could provide advantages for information transfer in the brain.

There are many distinct types of neurons in the brain, which are distributed in a highly organized fashion and interconnected with remarkable specificity. Such diversity of cell types is seen in different sensory modalities: vision, audition, smell, and also across different species from worms to flies to humans. This suggests an evolutionary fitness benefit of a very general nature.

What is the computational role of cell type diversity in a large population of neurons? One prominent hypothesis is termed efficient coding. It suggests that neurons in different sensory organs have evolved so that they transmit the maximal amount of information to downstream brain areas for further processing. I use this hypothesis to study the diversity of cell types in the retina of the eye. We have known for some time that there are about 20 different type of cells in the retina; some process light intensity, others process color or motion. I examine the benefits for the existence of ON and OFF cell types, where ON cells respond to increases in light intensity, while OFF cells respond to decreases in light intensity in the visual scene. Using a mathematical analysis,

I show that more information about what we see is transmitted to our visual cortex if we have ON and OFF cells than if we have only ON, or only OFF, cells.

To do the analysis, I computed the statistics of bright and dark contrasts in a large bank of natural images collected by fellow visual neuroscientists. I also used empirical measurements from colleagues in the lab on the realistic constraints in the cells that we study, i.e. the maximal or mean amount of activity in the cells. In addition to showing that having both ON and OFF cells is better than just having cells of one kind, I also derived predictions for what the properties of these cells should be. For instance, given a number of neurons in a population that all code for the same visual stimuli, at what light intensity should each cell become active, and at what firing rate?

My collaborators are now testing these predictions in the real experimental system using retina recording in the mouse. Revealing principles for cell type diversification in the retina will aid in understanding the benefits of cell type diversity in subsequent stages of the visual system and in other sensory systems.

Marc Nahmani, PhD

Department of Biology
Brandeis University

Structure and Function of an Inhibitory Circuit Regulating Critical Period Plasticity

The development and maturation of the human brain does not occur linearly. Some periods in development are associated with accelerated ability to acquire functionality. These are called "critical periods." Dr. Nahmani's research explores the ability of the mature brain to enter similar periods of accelerated plasticity during recovery from injury. This work has implications for designing therapeutic strategies to help patients recover from traumatic brain injury.

Critical periods are temporal windows for neuronal malleability during mammalian development that enable robust adaptation and recovery of brain circuit function. These changes are paralleled by another "critical period" for optimal recovery after acute brain injury and stroke, suggesting that converging mechanisms underlie these two periods of brain plasticity.

In this talk, I present an overview of my graduate and postdoctoral research on the influence of excitatory and inhibitory circuits on the opening and closing of the developmental critical period in visual cortex, and outline future studies aimed at illuminating the intriguing parallels between developmental and injury-induced critical periods. During my graduate career I developed a sought-after method to exclusively label the thalamic axons that compose the "ocular dominance columns" in visual cortex first described by Hubel & Wiesel (Nahmani & Erisir, JCN, 2005). Using this tool, we were able to show that the synapses from these axons responded to much more rapid changes in visual input than

previously thought, highlighting their importance during a critical period for plasticity in visual cortex (Coleman, Nahmani et al., J. Neuroscience, 2010). As a postdoctoral fellow, I dissected the specific mechanisms whereby fast-spiking inhibitory neurons contribute to the initiation of this critical period in the visual cortex (Nahmani & Turrigiano, J. Neuroscience, 2014) and analyzed how neuronal and homeostatic plasticity during critical periods might be recapitulated after injury in the adult brain (Nahmani & Turrigiano, Neuroscience, 2014).

In order to investigate the intriguing parallels between this developmental critical period and the "critical period" for recovery from acute injury, I have developed a new traumatic brain injury paradigm using a pressurized biodegradable fluorescent bead injection into the cortex. This method will provide a much-improved level of accuracy, injury localization, and cell-type specificity to traumatic brain injury research, and will for the first time allow for direct and immediate therapeutic drug release at the site of injury.

Jennifer Gutsell, PhD

Department of Psychology
Brandeis University

Resonating With Allies and Competitors: a Motivational Approach to How the Brain Processes Others' Inner States

How does our perception of the people around us affect our empathy for them? How often do members of society discuss events in terms of "us" and "them"? Are there neural networks responsible for our perception of differences with individuals who are not in groups we identify with? Dr. Gutsell's work examines how prejudice and social group membership affects the neural mechanisms underlying our perception and understanding of the other's actions, intentions and emotions.

People say that to gain a true understanding of another, one needs to put oneself into another's shoes and try to see the world through his or her eyes. The assumption here is that understanding comes from using one's own references and one's own body to simulate the experiences of the other. In recent years, neuroscience has supported these folk psychology notions of how we understand each other: Similar neural circuits are activated during the experience and the observation of actions and emotions, and such neural resonance is said to support action understanding, basic empathy, and interpersonal coordination.

In this talk, I presented a motivational approach to neural resonance and looked at how various factors that might increase or decrease motivational relevance of another person affects neural resonance. I presented research that uses the suppression of electroencephalographic (EEG) oscillations in the mu frequency band during action and emotion expression observation as an index of neural resonance. First, a review of studies suggests an in-group bias

in neural resonance recorded over sensory motor areas: People show mu-suppression in response to the actions of in-group members, but they do not show mu-suppression in response to the actions of ethnic out-group members, and this bias in neural resonance is aggravated with increasing prejudice and for disliked out-groups. I presented a series of studies that explore facilitating and hampering conditions for cross-group neural resonance, focusing on the role that motivational relevance plays in determining with whom to resonate and with whom not to. How much people resonate with out-group members is malleable and appears to depend on the motivational significance of the target person and the behavior in question.

Shantanu Jadhav, PhD

Department of Psychology
Brandeis University

Neural Activity Patterns Required for Learning and Memory-Guided Behavior

We always hear that practice makes perfect and repetition builds mastery. But why? How does a brain learn? Dr. Jadhav's research studies structures in the brain that effectively replay a behavior or memory during activity as well as during sleep. In order for learning to occur, it is critical that this neural activity pattern is not disrupted; in the presence of a disruption, learning is impaired.

The ability to form memories and use past experience to guide behavior is a remarkable capacity of the brain. The hippocampus and prefrontal cortex are critical structures involved in learning and memory. In rodents, hippocampal place cells are active during behavior both in the context of place fields during theta oscillations, where individual neurons fire in specific regions of space, as well as during sharp-wave ripples (SWRs), during which place cell sequences are replayed. To test the role of awake SWRs and associated replay processes in memory, these events were specifically disrupted in the hippocampus of awake behaving animals during spatial learning. This resulted in a specific impairment in a spatial working memory process

that required linking temporally and spatially distant experiences. These results provide a crucial causal link between a specific hippocampal physiological pattern of activity and learning. Further, they also point toward a role of SWR-associated prefrontal activity in support of spatial working memory. Indeed, prefrontal activity is modulated distinctly by both awake SWRs as well as theta oscillations during learning, indicating that these network states represent fundamental modes of communication between the prefrontal cortex and hippocampus during behavior.

The Volen National Center for Complex Systems Poster Session

The Volen Retreat features an opportunity for all Volen-affiliated faculty, postdoctoral fellows, graduate and undergraduate students to present a poster detailing their research. This is a forum for 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, 23 postdoctoral fellows and students presented posters at the Volen Retreat. The presenters and titles are as follows:

Presenter	Poster Title
Daniel Acker Marissa S. Kuzirian	Semaphorin4D Attenuates Seizure Severity in an in Vivo Mouse Model of Epilepsy
Jonathan Cannon	Sequence Generation by Spatiotemporal Cycles of Inhibition
Mugdha Deshpande Josiah Herzog	Altered Dendrite Morphology and Growth Factor Signaling in Animal Models of ALS
Yasmin Escobedo	Target-Cell Dependent Plasticity of Inhibitory Synapses in Mammalian Cortex
Sarah Haddad	Various Modulatory Substances Differentially Affect Stable Rhythmic Output Across Temperature
Vera Hapiak	The Molecular and Circuit Basis of Thermo Sensation in <i>Caenorhabditis Elegans</i>
Anna Hartmann	Characterizing Behavioral Responses of Adult Nematodes to Pheromone
Anne Joseph	CaMKIV: Queen of the Kinases
Katelyn Kenny	The Activity Dependent GTPase Rem2 Negatively Regulates Dendritic Complexity in Response to Sensory Experience
Zachary Knecht	Hygrosensation in <i>Drosophila</i>

Volen Center for Complex Systems Poster Session (Cont.)

Presenter	Poster Title
Chang Liu	Serotonergic Neurons Activity Re-Patterns Sleep Architecture in <i>Drosophila</i>
Aoife McMahon	Hijacking an Editing Enzyme to Reveal the Targets of RNA-Binding Proteins
Nate Miska	Synapse Type Specificity of Synaptic Scaling in Visual Cortical L4
Timothy O'Leary	Temperature Robust Neural Activity from Feedback Control of Ion Channel Expression
Sean O'Toole	Dicer Is Involved with Cortical Fast Spiking Interneuron Plasticity
Adriane Otopalik Philipp Rosenbaum	Spatial Mapping of Transmitter and Neuropeptide Responses in Single Identified Neurons
Marjena Popovic	Effects of Visual Training on Population Activity in V1
Sarah Richards	Knockout of Rem2 Impairs Experience Dependent Plasticity in Mouse Visual Cortex
Asuka Takeishi	The AWC and ASI Sensory Neurons Contribute to Starvation-Dependent Plasticity in Thermotaxis Behavior
Alexander Sutton	Quantifying Morphology of Stomatogastric Ganglion Neurons in <i>C. Borealis</i>

The M.R. Bauer Foundation Summer Science Research Fellowship

The M.R. Bauer Summer Science Research Fellowship Program completed its second summer in 2015. The M.R. Bauer Foundation generously supported Brandeis undergraduate Zoe Brown '16. Brown was able to perform research in the laboratory of Volen Center for Complex Systems' faculty member Art Wingfield. This opportunity allowed a very talented undergraduate to tackle an important question about how the brain processes speech. This summer's experience will form the basis of Brown's senior thesis. Below, Brown describes her summer 2015 research experience.

The Summer Undergraduate Research Fellowship was an invaluable experience. At the Memory and Cognition Lab at Brandeis University, I investigated the effect of speech prosody (word stress, pitch contour, and pauses) on speech recognition as measured by recall accuracy and, using pupillometry measurements, cognitive effort. For the duration of the fellowship, I ran all of the participants in the study and scored the data, and with the help of a graduate student, discussed how to analyze the data. Additionally, I made and presented a poster, "Examining the Behavioral and Physiological Effects of Prosody on Sentence Processing," at SciFest, a poster session at Brandeis.

During the study, young adults were asked to listen to and recall sentences, half of which contained prosody congruent with the syntactic structure, and the other half of which had been computer-edited to place the prosody in conflict with the syntax. Recall accuracy was significantly lower for the incongruent condition than for the congruent condition. For the incongruent

sentences, participants often shifted their responses to match the prosodic marking, which indicated that prosody often had a strong lure over the intended syntactic parse. To measure effort, pupil dilation was continuously recorded using an eye tracker and was time-locked to the sentences via MATLAB. Pupillometry data are currently being analyzed, and I expect that these data will provide a sensitive measure of cognitive effort. If so, as the incongruent condition produced more errors, there should be an overall larger pupil dilation, reflecting an increase in effort, for this condition.

Reading articles on previous research done on prosody and pupillometry, running each experiment, scoring and analyzing the data, and presenting the poster all helped strengthen my understanding of the conceptual basis of the project. It was very valuable to be able to work with the graduate student, the director of the lab (Art Wingfield), and other colleagues; the ability to obtain reliable results in a relatively short time period highlighted the importance of collaboration.

I am very grateful for this opportunity, and for the knowledge and experience I have gained from this fellowship. I am currently working on a follow-up study for this project. During the academic year, we plan to investigate whether age differences and hearing acuity affect the accuracy of recall and placement in the prosodic boundary in congruent and incongruent prosody. My long-term plans include graduate school and academic or clinical research, and this experience will be very helpful for my future plans.

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

