Brandeis University

Benjamin and Mae Volen National Center for Complex Systems

The M.R. Bauer Foundation Colloquium Series and Distinguished Lecturer Series

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The M.R. Bauer Foundation Colloquium Series and Distinguished Guest Lecturer Series 2012-2013 Summary

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The 2012-2013 M.R. Bauer Foundation Colloquium Series and Distinguished Guest Lecturer Series

Introduction

I am writing at my desk from an office that enjoys a broad view of campus. Words appear in my field of view on the screen, having been tapped on the keyboard, but I can still happily acknowledge the swaying trees and bright sun. I marvel at the machine—the brain—that allows me to conduct and appreciate these events.

And now, as you hold this brochure and contemplate these ideas, similar scenarios play out. You, and all of us connected with the Volen Center, are concerned with understanding how this can occur. How do we take in information and turn it into thoughts and feelings? What is it about the brain that makes this all possible?

This year's M.R. Bauer Foundation Colloquium and Guest Lecturer Series gives us, again, a unique opportunity to ask and answer these and many other questions, and to do so in celebration of the end of the Volen Center's second decade as a remarkable research facility. Thank you to all who supported, and continue to sustain, this scientific enterprise.

For almost 20 years, those of us affiliated with Brandeis and the Volen Center have benefitted from interdisciplinary alliances. The Volen Center's achievements in the past year alone—prestigious awards bestowed for seminal work, election of yet another member of the center to the National Academy of Sciences, appointment of a member to a presidential working group, among other successes—demonstrate the power of our collaborative approach.

These lectures and discussions provide another venue for cross-cutting engagement. The M.R. Bauer Foundation generously supports these dialogues to ensure that research is open to inquiry. We are grateful for the foundation's unyielding belief in the Volen Center and in the possibilities of our work.

Leslie Griffith, M.D., Ph.D.
Nancy Lurie Marks Professor of Neuroscience
Director, Volen National Center for Complex Systems

The M.R. Bauer Colloquium Series Summaries

Introduction

Astrophysicist Stephen Hawking (1941-) once stated, “I think the brain is essentially a computer, and consciousness is like a computer program.” Indeed, the complex processing of information that must occur within the human brain when a person performs even the most basic task, such as picking up a pencil, is very similar in outcome to the processing that occurs inside computers, allowing for results like the appearance of the words on this very page. Amazingly, all of this work goes on behind the scenes; the finished product, reflected in a behavior or in words on a screen, is all that we see. In order to understand how these outcomes are reached, it is necessary to understand the nuts and bolts that go into building the computer in the first place; in other words, how is the brain assembled such that it processes information in a meaningful way?

The human brain is comprised of billions of cells called neurons, which communicate with each other in networks that generate particular behavioral outcomes. An alternative name for these neuronal networks comes straight from the world of electronics and computers: circuits. Thus, an understanding of how these circuits within the brain are put together and how they function allows us to understand how the proper behavioral outcomes are reached. For example, one of the speakers detailed in the following pages explores the circuits that mediate vision within the brain. It turns out these circuits are very highly organized: subcircuits within subcircuits of neurons that function at different levels of visual processing. Studies like this are important and the complexity of the brain has never been clearer. In addition to this basic research, you will also read about the work of scientists who have been able to apply the basic principles of computational modeling to generate computer algorithms for how actual brain circuits work to perform particular processes. It is through their work that the idea of the brain as a computer is perhaps made most clear.

The 2012-2013 M.R. Bauer Colloquium series offered insights from six distinguished scientists on how the brain is assembled and how it processes information to produce behavioral outcomes. We have arranged the order of the colloquia in accordance with the approach each scientist uses to address this question: from hands-on experimental approaches to wiring up the circuit through computational modeling of how the circuit works. As in previous years, we have preceded each of the more technical summaries by a brief introduction, in italics, to place each presentation in the broader context of this year’s M.R. Bauer Colloquium Series theme: understanding how the wonderful machine that is the brain is assembled and functions in our daily lives.

Alex L. Kolodkin, Ph.D.
Solomon H. Snyder Department of Neuroscience
Howard Hughes Medical Institute
Johns Hopkins School of Medicine
(October 24, 2012)

Molecular mechanisms underlying the establishment of neural connectivity

How do you build a brain? This fundamental question in neuroscience is being addressed in the Kolodkin lab using the rodent visual system as a model. They have found that signaling between the molecules Sema6A and PlexA2 ensures that certain types of cells within the retina connect to appropriate neuronal targets in the brain, allowing the animal to perceive motion. Their work illuminates the precision of brain assembly at the most basic level.

Directing neurons (brain cells) to their appropriate targets during development, and forming appropriate synaptic connections between neurons to allow them to communicate, involves the action of extrinsic guidance signals. Research in the Kolodkin lab has addressed distinct cellular contexts in which a large family of guidance cues, proteins called semaphorins, regulate neural circuit assembly. In their present work, the lab asks how developing brain circuits achieve fidelity and specificity. This includes defining the extrinsic and also the cell-intrinsic mechanisms that underlie the guidance of neuronal processes to their intermediate and final targets, the pruning back of neuronal connections during development, the regulation of neuronal morphology, and the establishment of functional synapses, ultimately allowing neurons to communicate with each other. Semaphorins and their receptors serve all of these functions in living animals, and the Kolodkin lab's present work is directed toward understanding how unique neuronal responses to these cues are transduced.

One area of their work is to understand these issues in the mammalian visual system. Kolodkin's group has found that transmembrane semaphorins (including semaphorin 6A (Sema6A) and Sema5A/5B), which are proteins that are attached to the plasma membrane of neurons, play critical roles in regulating both select and more general aspects of the formation of the mouse retina. The lab's present analyses also include assessment of retinal ganglion cell (RGC, the neurons that send signals about the visual world to the brain) targeting to visual processing regions in the brain. Kolodkin's lab has found that, in addition to regulating the layered structure of the retina in a region known as the inner plexiform layer, Sema6A is also required for RGC targeting to the medial terminal nucleus (MTN), a center in the brain which receives input from a specific cell type known as ON direction-selective RGCs. In addition to characterizing how this RGC targeting progresses during visual system development, the lab has observed that PlexinA2 (PlexA2) serves as a Sema6A receptor in the retina, and possibly also binds to Sema6a in the context of RGC targeting to the MTN. Interestingly, Sema6A-/- mutant mice, which do not have the Sema6a protein, exhibit severe deficits in the optokinetic reflex (OKR), which is mediated by the MTN and thus demonstrates a critical role for Sema6A in this mode of motion detection.

Current experiments in the Kolodkin lab are directed towards understanding how Sema6A regulates both retinal and MTN targeting by dendrites and axons, respectively, of ON direction-selective RGCs. Taken together, the lab's work on visual system connectivity begins to define extrinsic contributions to the elaboration of neuronal connectivity and circuit formation during development, showing that a single guidance cue, Sema6A, apparently functions to organize several distinct components of a single visual system-dependent behavioral response.

Antoine Triller, D.Sc.
Director, IBENS (Institute of Biology
at Ecole Normale Supérieur) Paris
(March 6, 2013)

Synapse stability and plasticity: super-resolution and single molecule imaging

The brain processes information through communication between neurons (brain cells) at specialized sites called synapses. As you might imagine, no two synapses are exactly alike, despite the fact that they are comprised of many of the same types of molecules. The Triller lab uses high resolution imaging techniques to study synaptic variability, the changes that allow very similar synapses to convey very different types of information.

When neurons communicate at synapses, the variability of the response of the neuron receiving the signal (the postsynaptic neuron) following a single action potential (a form of electrical communication) from the neuron sending the signal arises from two sources: the fact that the release of neurotransmitter (the molecules that carry the signal) is not always the same, and the fact that the postsynaptic response to neurotransmitter release has variable timing and size.

At individual synapses, the number of molecules of a given type that are involved in these processes is small enough that the stochastic (random) properties of molecular events cannot be neglected. How the stochasticity of molecular processes contributes to the variability of synaptic signaling, and its sensitivity to and its robustness despite molecular fluctuations, has important implications for our understanding of the mechanistic basis of synaptic transmission and plasticity. Using the techniques of single-particle tracking and super-resolution imaging, the Triller lab addresses the issue of postsynaptic dynamics, including the interaction of neurotransmitter receptors (the proteins that receive the signal at synapses) with scaffolding proteins, and molecular regulations that are implicated in synaptic plasticity.

The combination of single particle tracking and super-resolution imaging methods allows the Triller lab open access to the number of molecules and energy involved in receptor-scaffold interactions, as well as the on and off rates of molecular interactions. Thus, these super-resolution methods will allow the lab to better understand the regulation of the number of postsynaptic receptors, and consequently that of postsynaptic responses.

Mark Frye, Ph.D.
Professor, Dept. of Integrative Biology and
Physiology and Howard Hughes Medical Institute
UCLA
(November 7, 2012)

Olfactory feature detection in flies

The major type of information that is received by the brain is sensory. What an animal sees, smells, hears, touches, and tastes are all used by the brain to allow that animal to make an appropriate behavioral response. The Frye lab studies how the sense of smell, olfaction, is used to influence the direction in which fruit flies choose to fly. Different odors tell the fly to come closer or stay away, and how the fly brain processes the information carried by those odors allows the fly to make an optimal decision.

Virtually all mobile animals are equipped with olfaction (a sense of smell), and are able to track chemical features of the world. Despite separation by 500 million years of evolution, there is great structural and functional similarity between insect and mammalian olfactory systems. This may be due in large part to the physics of fluid flow carrying the chemical molecules, which are similarly constrained for both groups. As such, many qualitative properties of chemotaxis behavior, the behavioral response of an animal to different odors, are shared among species. However, we have a remarkably incomplete understanding of the rules that define an odor feature, and that then transform this sensory perception into an adaptive behavioral response.

The Frye lab makes use of a virtual reality flight simulator equipped with an odor plume in which a single fly is suspended within a magnetic field, free to orient relative to the plume. Researchers can manipulate the type of odor the fly is exposed to, and might pulse it to produce some temporal pattern. They then manipulate the expression of olfactory receptor genes, thereby altering what the animal is able to smell. In combination, these techniques allow the Frye lab to identify how specific properties of a chemical feature, such as spatial intensity gradient (location), temporal pattern (timing), and hedonic valence (i.e. does it smell good or bad) define the tracking behavior of flies in motion, and through which signaling pathways. Finally, the flight simulator is surrounded by an electronic visual display, which researchers use to actively manipulate what the fly sees and investigate how well-known visual gaze stabilizing reflexes operating in flies and humans alike can be used to stabilize a flight path along an otherwise invisible and unstable chemical plume.

Rachel Wilson, Ph.D.
Professor of Neurobiology, Harvard University
and Howard Hughes Medical Institute
(October 3, 2012)

Olfactory processing in the *Drosophila* brain

How does the brain tell different odors apart? In the fruit fly brain, it turns out that particular pathways carry information about particular odors to different areas of a brain region known as the lateral horn. It is the overlap, or lack thereof, of these pathways that allows flies to distinguish between arrays of odors in their environment. This work from the Wilson lab nicely illustrates the diversity of circuitry that exists in the brain.

Chemicals in the environment are a rich source of information for living organisms. Odors carry signals about food, sexual partners, and potential dangers. Thus, the sense of smell is central to the ecology of many organisms. We know a considerable amount about how olfactory information is encoded in the first neurons to encounter a particular odor (olfactory receptor neurons), and the neurons that then receive this information first in the brain (the olfactory bulb in vertebrates and the antennal lobe in insects). Unfortunately, we know comparatively little about olfactory processing beyond this point. Specifically, there is relatively little known about how neurons in higher-order brain regions, beyond initial odor recognition, respond to odors, and less still about what specific features of olfactory stimuli they might encode.

Recent research from the Wilson laboratory has recently begun to map the pattern of direct projections from the *Drosophila melanogaster* (fruit fly) antennal lobe onto a higher brain area (the lateral horn). Their results show that the projections from specific olfactory processing channels are highly selective, and remarkably conserved across individuals. Some higher olfactory neurons respond to signals across several olfactory processing channels having overlapping odor selectivity. Other higher olfactory neurons respond rather selectively to one or a few processing channels, and are inhibited by others. These results demonstrate a diversity of higher-order olfactory computations, and they illustrate how these computations can arise from specific and stereotyped patterns of connectivity.

C. Randy Gallistel, Ph.D.
Professor of Psychology
Rutgers University
(October 10, 2012)

Memory and the computational brain

Many scientists hold the belief that the brain is like a machine, but it can be hard to figure out just how much like a machine it really is. Dr. Gallistel's work applies computational principles to model how the brain functions like a computer to produce particular behaviors. It turns out that memory in the brain is just as important as computer memory for reaching the desired outcome.

Cognitive scientists, who study the abstract mind, assume that memory stores facts about the experienced world in a computationally accessible form. Neuroscientists and connectionist modelers, who study the brain itself, assume that memory is a structural alteration wrought by experience in a dynamic brain. The rewiring of the brain by experience explains the effects of past experience on future behavior, but these alterations at synapses, the connections that allow brain cells to communicate, do not encode facts in a computationally accessible form. The neuroscientific view is not reconcilable with the computational theory of mind, which is the central doctrine of cognitive science. The question posed by Dr. Gallistel is: then, to which science should we look for guidance in thinking about the nature of memory in the brain, to cognitive science or to neuroscience?

Computation is defined mathematically as the composition of functions. Functions of arbitrarily many arguments may be achieved by the composition of 2-argument functions (e.g., addition, ordination, multiplication) but not by the composition of 1-argument functions (e.g., inversion). Thus, a computing machine, such as the human brain, must be capable of bringing an infinite number of different functions together with the machinery that effects their composition. The read-write memory makes possible the unlimited composition of functions. And, the addressability of memory locations enables variable binding and the formation of complex data structures.

Many simple animal behaviors imply the composition of functions in the brain. Examples discussed by Dr. Gallistel during his talk included dead reckoning, sun-compass orientation, course setting, and cache retrieval. These and many other examples imply that the brain has a yet-to-be-discovered addressable read-write memory. Dr. Gallistel argued that because this memory plays a central role in brain function, its discovery will transform neuroscience, and that memory is as important to computation as DNA is to life.

Dora Angelaki, Ph.D.
Wilhelmina Robertson Professor & Chair
of the Department of Neuroscience
Baylor College of Medicine
(April 24, 2013)

Merging of our senses: building blocks and canonical computations

Dr. Angelaki's work uses computational modeling and experimental approaches to show how the brain integrates sensory information to allow us to interact with the environment. Combining, say, visual information with vestibular (balance) information could be quite problematic unless the brain followed a very precise set of computational rules to process this information. Dr. Angelaki provides evidence that not only is the brain like a machine, but it's a very efficient one.

As we navigate through the world and interact with our environment, mental computations ensure that our body's orientation in space is maintained effortlessly, largely because of our sixth sense, our vestibular (balance) system. Brain circuits use an internal model of universal physical laws and the integration of information from all the senses to resolve ambiguities inherent in our sensors. Further, multisensory integration in the brain region known as the cortex with visual motion cues ensures improved precision of spatial perception. Both properties are predicted by a computational rule called Bayesian integration.

Spatial orientation, balance, and navigation depend on the ability to process motion information from the vestibular system, as well as to integrate this information with other multisensory cues and previous experiences. To achieve this, the brain faces two computational challenges. The first arises from a sensory ambiguity, because the otolith organs in the inner ear (which are responsible for our sense of balance) are equally sensitive to head tilt relative to gravity and to linear acceleration. As pointed out by Albert Einstein over a century ago, this uncertainty arises from the laws of physics and, unless corrected by the brain, this sensory ambiguity can be extremely problematic. In her talk, Dr. Angelaki summarized recent theoretical and experimental work that explains how the brain relies on three-dimensional calculus and multisensory fusion to compute an estimate of motion through an internal model of physical laws. Brain correlates of these computations are found within a brainstem-cerebellar network, regions of the brain where multimodal signals are combined both temporally and spatially to provide an internal estimate of gravity and linear acceleration. Dr. Angelaki applied Bayesian framework to show that these computations are performed optimally, taking into account both cue reliability and existing knowledge of the statistics of common experiences.

The second challenge arises from the necessity to integrate information from different sensory modalities to achieve a single unified perception. Optimal integration models predict that the benefit of multisensory integration depends on the relative reliability of the cues. The Angelaki lab explores multisensory cue integration for heading perception using both visual and vestibular signals. A brain correlate of this interaction during a type of behavior known as heading direction discrimination task was found in the activity of single neuron cells in the macaque monkey visual cortex, the brain region responsible for visual processing. Neurons with congruent (matching) preferences for visual and vestibular stimuli showed improved sensitivity. These findings provide the first behavioral demonstration of statistically-optimal cue integration in non-human primates and identify a population of neurons that may form its basis in the brain.

The M.R. Bauer Distinguished Lecturer Series Summaries

Introduction

Every year the M.R. Bauer Distinguished Lecturer program brings to campus two distinguished visitors who spend a full week at Brandeis. These 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 Amita Sehgal from the Perelman School of Medicine at the University of Pennsylvania, and Edward Callaway from the Salk Institute.

Amita Sehgal, Ph.D.
Professor, Department of Neuroscience/Howard
Hughes Medical Institute
Perelman School of Medicine at the
University of Pennsylvania
(Week of December 12, 2012)

What controls sleep? Using a fly to determine the molecular underpinnings

Our first week-long visitor, Dr. Amita Sehgal, uses the fruit fly as a model system to study how the brain works during sleep and how it produces daily behaviors. Among the many findings that she discussed, the Sehgal lab has identified a gene called sleepless that seems to be important for the onset of sleep. Mutant flies in which sleepless doesn't function have trouble falling asleep because the activity of a particular subset of neuronal networks remains high. This is evidence that whether you are awake or asleep is influenced by which neuronal networks are active at a given point in time.

Sleep remains one of the big mysteries of life, with little known about why we sleep and what causes the sleepiness that occurs after prolonged wakefulness. Given that animals are more susceptible to predators when they are asleep, it is generally agreed that sleep must confer important benefits that account for its selection during evolution. We know that humans deprived of sleep show impairments in performance, specifically in vigilance and in cognitive tasks, indicating that at least one function of sleep is to promote functioning of the nervous system. Indeed, sleep disruption is thought to be the cause of human error in some major, well-known catastrophes. However, short sleep times have also linked to metabolic defects, which suggests that sleep affects whole animal physiology.

The fruit fly, *Drosophila melanogaster*, has served as an excellent model to decipher the genetic and molecular basis of many processes, including circadian rhythms: the molecular nature of this biological clock that drives a 24 hour rhythm in many processes, including rest/sleep, was elucidated in *Drosophila*. Based upon the success of the *Drosophila* model in identifying mechanisms that time behavior and physiology, the Sehgal lab sought to use it to understand a specific circadian-regulated behavior, sleep. They showed that what was previously considered rest in *Drosophila* is actually a sleep state, and have since directed their experiments towards understanding how and why there exists a drive to sleep. Sehgal's group and other researchers have found that neurotransmitters and drugs that modulate human sleep have similar effects in flies. Thus, *Drosophila* can be used to identify novel sleep-altering drugs, and the lab has conducted a study to this effect.

A major advantage provided by *Drosophila* is the ability to conduct unbiased genetic screens; in other words, to search for genes required for a process of interest without any assumptions about the nature of molecules required. Through such a screen for sleep-altering genes, the Sehgal lab identified a gene they named *sleepless (sss)*. Animals lacking this gene showed a tremendous reduction in sleep, indicating that *sss* is essential for sleep to occur. The Sehgal lab found that the *sleepless* protein (SSS) normally promotes activity of a voltage-gated potassium channel, Shaker, which functions to silence the activity of neurons that would otherwise be communicating. In the absence of SSS, Shaker is downregulated and the activity of these neurons remains high. Sehgal suggested that this increase in neural activity, either directly or indirectly, prevents the onset of sleep. Recent studies in humans support a role for potassium channels in sleep, suggesting that this mechanism identified in *Drosophila* is conserved across species.

Edward Callaway, Ph.D.
Professor of Systems Neurobiology
The Salk Institute for Biological Sciences
(Week of April 10, 2013)

Of mice and monkeys: a journey into the visual system

Our second week-long visitor, Dr. Edward Callaway, uses vertebrate model systems including rodents and monkeys to study how the brain processes visual information. Dr. Callaway described a new technique developed in his lab that allows them to observe single connections between two neurons (brain cells), a scale that is very difficult to achieve. This technique allow the lab to see how the areas of the brain responsible for vision are organized; as it turns out, this is a complex issue, with the brain divided into circuits and subcircuits responsible for processing different types of visual information (i.e. motion).

During Dr. Callaway's visit, he took us on a journey through studies of the monkey and mouse visual system that have been conducted in his lab over the last 17 years. He first described experiments that were aimed at understanding how local neuronal signaling circuits in the monkey primary visual cortex, a region of the brain which processes visual information, integrate information from parallel input streams, and redistribute this information to other visual areas. These studies illustrated how difficult and tedious it has been to use traditional methods to address detailed questions about how local neuronal connections in the cortex relate to visual function.

Dr. Callaway then discussed studies demonstrating that cortical connections are cell-type specific, and that there are fine scale subcircuits embedded within the cortex. These observations illustrate the need for a new generation of molecular and genetic tools that have been developed in recent years that allow studies linking brain circuits to function at the level of cell types and even single neurons. He went on to describe a rabies virus based mono-transsynaptic tracing system that has been developed in his lab, allowing for the visualization of a single connection between two neurons in a particular signaling circuit or of a particular cell type. This new generation of molecular and genetic tools can at present be used most powerfully in mice, where it is more straightforward to restrict gene expression to cell types than in monkeys. The Callaway lab is therefore both developing better tools for genetic targeting of cell types in monkeys, and conducting studies of the organization and function of the mouse visual system. They have used techniques such as intrinsic signal imaging and 2-photon calcium imaging to demonstrate functional retinotopic maps in visual centers in the mouse brain, meaning these regions receive precisely organized information about the visual world from the retina and accurately represent the world through their activity. These techniques have allowed the Callaway lab to functionally characterize the neurons in seven areas of the brain responsible for vision. These observations reveal both parallels and differences between the functional organization of visual areas in mice and monkeys and lay the ground for future studies that allow the genetic tools in mice to be used to study how local neuronal signaling circuits mediate interactions between different brain regions.

Acknowledgments

As always, we thank the speakers who came to the Brandeis campus this past year to share with us their research, and to engage in many hours of stimulating discussion and exchanges of ideas with Volen Center faculty, graduate 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 one of our graduate students in neuroscience, Amy E. Ghiretti, for her valuable contribution and editorial assistance in the preparation of this report.

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

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