Brandeis University

The Volen National Center for Complex Systems

The M.R. Bauer Foundation Colloquium Series and Scientific Retreat

August 1998

Introduction

The 1998 M.R. Bauer Foundation Colloquium Series and Scientific Retreat

Brandeis University

Benjamin and Mae Volen National Center for Complex Systems

As the Director of the Volen National Center for Complex Systems at Brandeis University, it is my pleasure to present the proceedings of The M. R. Bauer Colloquium Series. The Colloquium Series has completed its fourth stimulating and successful year, as a result of the Bauer Foundation's continued and generous support. The 1997-98 series included presentations on topics ranging from using animal models to unlock the secrets of amyotrophic lateral sclerosis (ALS; also known as *Lou Gehrig's Disease*) to focusing on micro and macro perspectives on cognitive aging. Our guest lecturers represent some of the most prestigious institutions in the world including Harvard University, Duke University Medical Center, The University of Leicester, and The Johns Hopkins University School of Medicine.

The 1998 Volen Center Retreat, sponsored by the M. R. Bauer Foundation, was held on March 5-6, 1998 at the Marine Biological Laboratory in Woods Hole, Massachusetts. This year's theme, "The Center for Complex Systems: The Next Generation," highlighted the work of past postdoctoral researchers who are now faculty at other distinguished institutions, as well as current Brandeis postdoctoral candidates. Our keynote speakers were Peter Reinhart, Ph.D., Department of Neurobiology, Duke University Medical Center, and Charalambos Kyriacou, Ph.D., Department of Genetics, University of Leicester, who spoke on "Ingredients for neuronal coincidence detection: a calcium/protein kinase/ion channel soufflé" and "Evolution and clock genes," respectively. All of the scientists who participated in the retreat gave very impressive talks about their research to approximately 130 scientists and students who had gathered for this annual two-day event.

The Volen Center at Brandeis was created to promote interdisciplinary exploration of neural and cognitive sciences, including learning and memory. The intense interactions of researchers with different backgrounds within the Center make it a unique resource for neuroscience research. The Bauer Colloquium Series and Retreat have been extraordinarily successful in promoting academic exchange and professional growth at the Volen Center and within the Brandeis community for the past four years. Support from the Bauer Foundation has been instrumental in exposing students and faculty to current research being conducted by other scientists, within the University and from other institutions. The colloquia, in conjunction with the annual retreat, enable accomplished researchers from other academic institutions and corporations to present their latest findings and to discuss this information with the Volen Center faculty and students.

Laurence F. Abbott
Nancy Lurie Marks Professor of Neuroscience
Director, Volen National Center for Complex Systems

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Timothy Salthouse, Ph.D.
Professor of Psychology
Georgia Institute of Technology
Atlanta, Georgia
October 9, 1997

Micro and Macro Perspectives on Cognitive Aging

Moderately large negative relations between age and measures of certain types of cognitive functioning have been documented for over 80 years. In the last several decades the dominant approach to explaining these age-related differences has been to attempt to isolate the source of the age-related differences in a specific component of processing. This approach can be called the micro perspective because it is focused on interpreting the age-related differences in cognition in terms of effects on constituent elements of the task. An alternative approach that has recently been growing in usage has emphasized the interrelations of age-related effects on different variables. Because the focus in this approach is at a broader level than individual variables, and is concerned with determining the extent to which age-related influences on the target variable are independent of the effects on other variables, it can be called the macro perspective. Examples of research from both perspectives are described in this talk, and a proposal is offered for how future research could combine the analytical aspects of the micro perspective and the integrative aspects of the macro perspective.

Peter L. Strick, Ph.D.
Professor of Physiology
V.A. Medical Center
Syracuse, New York
November 10, 1997

Basal Ganglia and Cerebellar "Loops" with the Cerebral Cortex: Motor and Cognitive Circuits

The basal ganglia and cerebellum are major subcortical nuclei that have long been regarded as critical to the generation and control of movement. A hierarchical scheme of organization can be used to describe the internal circuitry in both groups of nuclei. The "input layer" of basal ganglia processing is represented by the caudate and putamen. The functionally analogous level in cerebellar circuits is represented by specific pontine nuclei that send "mossy fiber" inputs to cerebellar cortex. The input layers of both circuits receive signals from diverse regions of the cerebral cortex, including motor, sensory, posterior parietal, prefrontal, cingulate, and temporal areas. The "output layer" of basal ganglia processing is represented by the internal segment of the globus pallidus and the pars reticulata of the substantia nigra; comparable structures for the cerebellum are the three deep cerebellar nuclei: dentate, interpositus, and fastigial. Neurons in the output layers of both circuits send their axons to the thalamus and, by this route, project back onto the cerebral cortex. Thus, a major structural feature of basal ganglia and cerebellar circuits is their participation in multiple loops with the cerebral cortex.

Our understanding of the organization of basal ganglia and cerebellar loops with the cerebral cortex has evolved considerably over the last 20 years. In the past, basal ganglia and cerebellar output was thought to terminate in a single region of the thalamus and influence a single cortical area, the primary motor cortex. According to this view, basal ganglia and cerebellar loops served to collect signals from motor, sensory, and cognitive areas of the cerebral cortex and "funnel" this information into the motor system to generate and control movement.

In recent years, this "classical" view of basal ganglia and cerebellar function has been challenged. A number of anatomical studies has demonstrated that basal ganglia and cerebellar output terminates in multiple thalamic nuclei, and that these thalamic nuclei project more widely in the cerebral cortex than previously suspected. As a consequence, there is a growing awareness that basal ganglia and cerebellar output may influence *non-motor*, as well as motor areas of the cerebral cortex. For example, we proposed that the basal ganglia participate in at least five separate loops with the cerebral cortex (Alexander, DeLong and Strick, 1986). These loops were designated the skeletomotor, oculomotor, dorsolateral prefrontal, lateral orbitofrontal, and anterior cingulate circuits. Based on this scheme, basal ganglia output was thought to influence not only the generation and control of movement, but also the higher order functions subserved by prefrontal, orbitofrontal and cingulate cortex.

Similarly, Leiner et al. (1986, 1991, 1993) have suggested that cerebellar output is directed to prefrontal, as well as to motor areas of the cerebral cortex. They noted that, in the course of hominid evolution, the lateral output nucleus of the cerebellum—the dentate—undergoes a marked expansion that parallels the expansion of cerebral cortex in the frontal lobe. They argued that the increase in the size of the dentate is accompanied by an increase in the extent of the cortical areas in the frontal lobe that are influenced by dentate output. As a consequence, they proposed that cerebellar function in humans has expanded to include involvement in certain language and cognitive tasks.

Until recently, it has been difficult to evaluate the validity of these proposals because of the relative paucity of experimental data on the actual cortical "targets" of basal ganglia and cerebellar output. To overcome this problem, we developed a novel neuroanatomical technique for tracing circuits in the central nervous system of primates (Zemanick et al., 1991; Strick and Card, 1992; Hoover and Strick, 1993; Middleton and Strick, 1994, 1996; Kelly and Strick, 1997). The technique uses retrograde transneuronal transport of specific strains of neurotrophic viruses (e.g., herpes simplex virus type 1 and rabies) to label chains of synaptically linked neurons. For example, two to three days following injections of HSV1 into the primary motor cortex, the virus is taken up and transported in the retrograde direction to label the cell bodies of neurons in the ventrolateral thalamus that innervate the injection site. After four to five days, the virus is then transported *transneuronally* in the retrograde direction and labels neurons at subcortical sites that project to the ventrolateral thalamus, i.e., output nuclei in the basal ganglia and cerebellum. Thus, this technique enables one to map basal ganglia-thalamocortical and cerebello-thalamocortical pathways of primates.

To date, we have used trans-neuronal transport of neurotropic viruses to examine basal ganglia and cerebellar loops with skeletomotor, oculomotor, prefrontal and inferotemporal areas of the cerebral cortex. In addition, we have performed physiological studies to examine the non-motor functions of basal ganglia and cerebellar output. Overall, our results indicate that concepts about basal ganglia and cerebellar function should be expanded to include their participation not only in motor control, but also in aspects of cognition and even higher-order visual processing. Our observations indicate that widespread regions of the prefrontal cortex thought to be involved in "executive" functioning are the target of basal ganglia and cerebellar output.

These results have broad clinical implications. For example, there is now considerable evidence that a variety of neuropsychiatric disorders such as schizophrenia, autism, Tourette's syndrome, and obsessive-compulsive disorder are associated with alterations in basal ganglia and/or cerebellar function. It is possible that alterations in the function of specific basal ganglia and cerebellar loops lead to an identifiable set of neuropsychiatric symptoms. Thus, information on basal ganglia and cerebellar loops with the cerebral cortex may provide a new anatomical framework for understanding the contributions of these structures to mental, as well as motor function.

Donald I. Price, M.D.
Professor of Pathology
The Johns Hopkins University School of Medicine
Baltimore, Maryland
November 24, 1998

Lou Gehrig's Disease: Lessons from Animal Models

The human neurodegenerative diseases, including amyotrophic lateral sclerosis (ALS) and Alzheimer's disease (AD), are adult-onset, chronic, progressive disorders whose clinical features reflect the vulnerability of specific populations of neurons in each disease. In ALS, weakness and atrophy reflect dysfunction/death of motor neurons; in AD, memory loss and dementia are the result of neurofibrillary tangles, Aβ42 amyloid deposits, and death of neurons in basal forebrain, hippocampus, and cortex. Subsets of cases of familial ALS (FALS) and AD (FAD), often show dominant inheritance; some cases of FALS are linked to mutations in the superoxide dismutase 1 (SOD1) gene; and some pedigrees with FAD exhibit mutations in genes encoding either the amyloid precursor protein (APP) or presenilins (PS1 and PS2). Much has been learned about the biology of these mutant transgene products by recent *in vitro* and *in vivo* studies. This lecture describes some of this work, with particular emphasis on exciting advances from studies of transgenic (Tg) mice that show many features of these human disorders.

Amyotrophic Lateral Sclerosis and Tg Models

ALS is characterized by paralysis, muscular atrophy, spasticity, and a variety of other motor signs; electrodiagnostic studies disclose evidence of denervation of muscle. Weakness and atrophy are related to abnormalities of large α-motor neurons of the brainstem and spinal cord, and spasticity reflects alterations in upper motor neurons. Lower motor neurons show a variety of abnormalities including ubiquitin and phosphorylated neurofilament immunoreactivities in cell bodies and swollen axons (spheroids) with maloriented arrays of neurofilament. In some cases of SOD1-linked FALS, motor neurons may also contain SOD1-immunoreactive intracytoplasmic inclusions. It has been estimated that 10 percent of adult-onset cases of ALS are familial with autosomal dominant inheritance and age-dependent penetrance. Approximately 20 percent of cases of FALS are linked to mutations in SOD1, a member of a family of metalloenzymes that acts as a free radical scavengers.

Recently, several groups of investigators produced Tg mice with FALS-linked SOD1 mutations. Lines of Tg mice that express the G37R HuSOD1 mutation at 3-12x levels of endogenous SOD1 in the spinal cord invariably develop progressive motor neuron disease. At four months of age, these Tg mice begin to show reduced spontaneous movements, difficulty moving their hindlimbs, and muscle wasting; eventually, forelimbs become weak, and hind limbs are completely paralyzed. Electromyographic patterns and muscle biopsies show features identical to those documented in patients with ALS. G37R HuSOD1 mice have significantly elevated levels of SOD1, and activity gels show increases in SOD1 activity, confirming that the G37R mutation synthesized *in vivo* retains full specific activity. In mice that express mutant SOD1, motor axons accumulate SOD1 immuno-reactivity. In motor neurons, SOD1 is transported anterograde in axons as part of the slow component. Recent studies in Tg mice expressing mutant SOD1 have shown the toxic protein is transported into axons. In the early preclinical period, motor axons as well as some dendrites exhibit very small vacuoles, usually associated with enlarged degenerating mitochondria and swollen endoplasmic reticulum. Subsequently, cell bodies show abnormal patterns of ubiquitin and phosphorylated neuro-filament immunoreactivities. Motor axons, some of which develop abnormalities of the cytoskeleton, undergo Wallerian degeneration; muscle fibers are denervated.

The observation that Tg mice expressing mutant SOD1 show no loss of enzymatic activity yet develop the disease strongly suggests that, at least for these mutations, SOD1-linked FALS is caused by the gain of a toxic property by the mutant enzyme. This concept is supported by several other lines of evidence: some mutant SOD1 possess near-normal levels of enzyme activity/stability *in vitro* and/or restore SOD1 null yeast to the wild-type phenotype but accelerate the death of nerve cells *in vitro*; SOD1 mutations do not have a dominant negative effect on wild-type SOD1; and wild-type HuSOD1 Tg mice do not develop overt motor neuron disease. SOD1 null mice develop normally and do not develop a FALS-like disease. A major question in the field is the nature of the toxic properties acquired by mutant SOD1 and the mechanisms of cell injury: one hypothesis is that a peroxidase activity by mutant SOD1 catalyzes conversion to H_2O_2 to OH, which is capable of oxidizing a variety of targets; and a second hypothesis is that mutant SOD1 has the enhanced ability to utilize peroxynitrite to form nitronium ions that can nitrate tyrosine residues. Both of these hypotheses are consistent with the premise that FALS mutations alter protein structure in such a way that mutant SOD1 has

a toxic effect on substrates critical for the survival of motor neurons. Because SOD1 is abundant in spinal motor neurons and transported anterograde in axons, we have suggested that the toxic mutant protein damages a variety of molecular targets with significant consequences for motor neurons.

Alzheimer's Disease and Tg Models

AD, the most common cause of senile dementia, is the result of selective vulnerability of subsets of neurons and the presence of neurofibrillary tangles, Aβ amyloid deposits, and death of nerve cells in the basal forebrain, hippocampus, and cortex. Risk factors for AD include: age; mutations in APP and PS1 and PS2 genes, which cause autosomal dominant disease; and the presence of apolipoprotein E4 allele, which is a susceptibility factor. Animal models are critical for investigating a variety of processes that involve normal brain function, for analyzing the mechanisms of disease-related abnormalities *in vivo*, and for testing novel therapies. The character, evolution, and mechanisms of some of the cellular abnormalities in AD have been clarified in studies of aged monkeys and Tg mice that overexpress mutant transgenes. Both aged nonhuman primates and APP and APP-PS1 mutant Tg mice show cellular abnormalities, including neuritic plaques consisting of dystrophic neurites and deposits of Aβ42 (a putative toxic peptide) similar to those that occur in individuals with AD. *In vitro* and *in vivo* studies have shown that different APP mutations increase the amount, length, and fibrillogenic properties of Aβ. PS1 mutations influence APP processing and increase levels of Aβ42 and accelerate amyloidogenesis *in vivo*. Tg mice overexpressing mutant APP transgenes show increased ratios of Aβ42:40 and develop Aβ deposits in the cortex and hippocampus. Recently, we have examined the extent and frequency of Aβ deposits in: 12-month-old Tg mice that coexpress HuPSI-A246E and APPswe: mice that coexpress wild-type HuPS1-and APPswe: mice that express APPswe alone; and mice that express mutant PS1 alone. In double Tg mice, coexpression of HuPS1-A246E with APPswe reduces the interval of the formation of initial Aβ deposits from 12 months in mice expressing APPswe alone to less than nine months in mice expressing APPswe with HuPS1-A246E. These data provide evidence to support the hypothesis that a principal pathway by which mutations in PS1 predispose individuals to FAD is to accelerate Aβ deposition.

Conclusion

Enormous progress has been made in understanding these neurodegenerative diseases. In particular, Tg model systems provide extraordinary opportunities to clarify some of the mechanisms leading to cellular abnormalities that occur in ALS and AD and to define some of the pathogenic pathways that represent targets for therapy. Finally, these models are critical for testing novel treatment strategies that, if effective in animals, can be rapidly introduced into human clinical trials.

Daniel L. Schacter, Ph.D.
Professor of Psychology
Harvard University
Cambridge, Massachusetts
January 15, 1998

The Cognitive Neuroscience of Illusory Memories

Beginning with pioneering studies of Sir Frederic Bartlett, psychologists have been aware that memory is a constructive process that is sometimes prone to distortions and illusions. In contrast, until recent years neuropsychologists and neuroscientists interested in brain substrates of memory have paid little attention to illusions and distortions that illuminate constructive remembering. This presentation focuses on recent research concerning illusory memories in amnesic patients and older adults, and concludes by considering relevant evidence from neuroimaging studies.

To investigate false recognition in amnesic patients, Schacter, Verfaellie, & Pradere (*J. Mem. & Lang.*, 1996) used the Deese paradigm, recently revived by Roediger and McDermott (*JEP: LMC,* 1995). After studying such associates as *candy, sour, sugar, bitter* and other related words, people frequently falsely recognize the nonpresented associate *sweet.* We found that amnesic patients showed—as expected—reduced levels of veridical recognition memory compared to a control group, making fewer hits to studied words and more false alarms to unrelated nonstudied words than did controls. More importantly, amnesic patients made fewer false alarms than controls to nonstudied associates such as *sweet.* This latter finding suggests that false recognition of nonstudied associates depends on retention of semantic information that also supports veridical recognition of presented words. More recent findings indicate that amnesic patients also show reduced levels of false recognition when tested with words that are perceptually similar to previously studied words (Schacter, Verfaellie, & Anes, *Neuropsychology,* in press). Taken together, the two sets of studies suggest that medial temporal/ diencephalic structures that are damaged in amnesic patients play a role in the encoding and/or retrieval of gist or general similarity information that drives false recognition.

In contrast to these findings, we have found that older adults, despite showing less accurate veridical recognition than younger adults, are relatively more susceptible to false recognition of semantic associates (Norman & Schacter, *Mem. & Cognit.*, in press). We have also documented an age-related increase in susceptibility to false recognition of nonpresented pictures that are perceptually/ conceptually similar to previously studied pictures (Koutstaal & Schacter, *submitted*, 1997).

Recent neuroimaging data provides further insight into these findings. Using PET and fMRI, we have found robust activation of anterior prefrontal cortex during false recognition, with some evidence relating these activations to post-retrieval monitoring activities (Schacter, Reiman, et al., *Neuron*, 1996; Schacter, Buckner et al., *Proc. Cog. Neurosci. Soc.,* 1997). Other PET studies indicate that older adults sometimes fail to show normal activation of anterior prefrontal regions (Schacter, Savage et al., *NeuroReport,* 1996). Thus, age-related increases in susceptibility to false recognition may depend in part on faulty monitoring processes that depend on prefrontal regions. In contrast, PET data indicate that medial temporal regions are related to successful conscious recollection in younger and in older adults (Nyberg et al., *Nature*, 1996; Schacter, Savage et al., 1996). Combined with the data showing reduced false recognition on amnesic patients, these results imply that medial temporal activity is important for veridical and illusory recollections.

Vernon Mountcastle, D.Sc., M.D.

Professor
Krieger Mind/Brain Institute
The John Hopkins University
Baltimore, Maryland
March 26, 1998

A major research program in neuroscience is to determine the relations between the material order of the world around us and the sensory-perceptual order of our experience; and, to discover the central neural mechanisms of these transformations. Our perceptual experiences are generated by the integration of the central neural activity set in motion by sensory stimuli with the activation of the neural images of past experience, and with those of the current central brain state. This combination is a construction. The general problem of determining the neural basis of these constructions, and of the brain mechanisms in perception, can now be studied in a variety of experiments in which perceptual experiences and the underlying neural activities are observed directly. This is presently the most successful experimental paradigm used in perceptual neuroscience.

I consider in this lecture two of the many sets of unsolved problems in the cortical mechanisms in perception. First, the unknown functional operations in the operation of small cortical modules; and, second, the unknown functional operations in the large-scale distributed systems of the cerebral cortex.

I considered a number of sources of knowledge that bear directly upon these problems; I list them here as questions with answers.

1. What have phylogenetic and comparative studies contributed to knowledge of the dynamic function of the cerebral cortex? Answer: Nothing.

2. What have anatomical studies contributed to knowledge of the intrinsic or systems operations within the neocortex? Answer: They provide the framework for a future knowledge of operations, but nothing more.

3. What have studies of cortical "functional organization" contributed to understanding its intrinsic function? Answer: Nothing.

4. What have studies of the ontogenesis of the cerebral cortex contributed to understanding its function? Answer: Nothing.

5. What have studies of synaptic transmission contributed to knowledge of the dynamic actions in cortical microcircuits and distributed systems? Answer: A great deal, the fundamental knowledge to build on.

6. What have imaging studies contributed to understanding dynamic cortical function? Answer: Nothing.

I then summarized the present state of knowledge of the properties of cortical microcircuits, with the conclusion that these operations are emergents, and cannot be predicted from the properties of their cellular constituents. The lecture closed with some speculations about the methods that may be of value in studies of these problems.

Mu-ming Poo, Ph.D.
Steven W. Kuffler Professor of Biology
University of California, San Diego
La Jolla, California
May 1, 1998

Propagation of synaptic modifications in neural networks

In vivo whole-cell recording from developing Xenopus tectal neurons revealed that convergent retinotectal synapses undergo persistent homo- and heterosynaptic modification following correlated pre- and postsynaptic activity within a narrow time window. Synaptic inputs that are repetitively activated within 20 ms before the spiking of the tectal neuron become potentiated, while subthreshold inputs activated within 20 ms after the spiking become depressed. Thus the initial synaptic strength and the relative timing of synaptic activation are critical for activity-dependent cooperation and competition between convergent retinotectal inputs in the developing optic tectum.

The 1998 Volen National Center for Complex Systems Scientific Retreat

The Center for Complex Systems: "The Next Generation"

Marine Biological Laboratory
Woods Hole, Massachusetts
March 5-6, 1998

The Center for Complex Systems: "The Next Generation"

On March 5 and 6, 1998, the Volen National Center for Complex Systems held its annual scientific retreat. This year the retreat titled "The Next Generation," highlighted the excellent work done by our postdoctoral fellows. On Thursday evening the two keynote speakers were former postdocs at Brandeis. Both have gone on to highly successful research and academic careers. On Friday, our six lecturers were current postdoctoral fellows. They made terrific presentations, which highlighted the high caliber of people and research taking place within the Center.

Approximately 130 people attended this year's retreat, which was held at the Marine Biological Laboratory (MBL) in Woods Hole, Massachusetts. The MBL facility includes lecture halls, function rooms, cafeteria-style dining, and overnight dorm room accommodations. Bringing the researchers (faculty, postdocs, and students) together off-campus for a 24-hour retreat was again tremendously successful. The MBL provides a stimulating environment for interactions as well as a scenic site for walking and relaxing.

March 5, 1998

2:00 pm
Arrival and check-in

4:30 pm
Poster session and refreshments

6:00 pm
Dinner

7:00 pm
Keynote Speakers
Peter Reinhart, Ph.D.
Department of Neurobiology
Duke University Medical Center
Durham, North Carolina
"Ingredients for Neuronal Coincidence Detection: A Calcium/ Protein Kinase/Ion Channel Soufflé"

Charalambos Kyriacou, Ph.D.
Department of Genetics
University of Leicester
Leicester, United Kingdom
"Evolution and Clock Genes"

9:00 pm
Music and dancing

March 6, 1998

7:00-8:30 am
Breakfast

8:30 am
Jorge Golowasch, Ph.D.
Department of Biology and Volen Center for Complex Systems
Brandeis University
Waltham, Massachusetts
"Activity-Dependent Regulation of Conductances and Network Properties"

9:00 am
Alan Bawden, Ph.D.
Computer Science Department and Volen Center for Complex Systems
Brandeis University
Waltham, Massachusetts
"Linear Names: Glue for Network Computing"

9:30 am
Joan Rutila, Ph.D.
Department of Biology
Brandeis University
Waltham, Massachusetts
"Genetic and Behavioral Analysis of a New Rhythm Mutant in Flies"

10:00 am
Break

10:30 am
Niraj Desai, Ph.D.
Department of Biology
Brandeis University
Waltham, Massachusetts
"Activity-Dependent Regulation of Cortical Activity"

11:00 am
Debra Titone, Ph.D.
Department of Psychology and Volen Center for Complex Systems
Brandeis University
Waltham, Massachusetts
"Contextual Sensitivity in Language Comprehension"

11:30 am
Todd Holmes, Ph.D.
Department of Biochemistry and Volen Center for Complex Systems
Brandeis University
Waltham, Massachusetts
"Reciprocal Regulation Phosphotyrosine and Potassium Channel Signaling"

12:15 pm
Lunch

1:00 pm
Departure

Peter Reinhart, Ph.D.
Professor of Neurobiology
Duke University Medical Center
Durham, North Carolina
March 5, 1998

Ingredients for Neuronal Coincidence Detection: A Calcium/Protein Kinase/Ion Channel Soufflé

A central theme common to current models of neural plasticity is that protein phosphorylation/ dephosphorylation of one or more synaptic proteins leads to a use-dependent alteration in the electrical properties of neurons. Although the identity of the molecular species mediating such plasticity have not been identified, K_{Ca} channels represent a likely target due to their predominantly presynaptic location, and their ability to act as feedback regulators of the voltage-activated Ca^{2+} channels involved in NT release. These properties endow presynaptic K_{Ca} channels with the ability to regulate the duration of the presynaptic action potential, and hence, indirectly modulate the presynaptic Ca^{2+} concentration. Such regulation modulates the amount of neurotransmitter released from presynaptic terminals.

K_{Ca} channels are also expressed in cell bodies, and in postsynaptic terminals, locations known to contain a number of other Ca^{2+}-permeable channels such as some types of NMDA and AMPA receptors. If K_{Ca} channels are positioned close to such Ca^{2+}-permeable channels in the membrane then they will be activated by the entry of Ca^{2+}. The resulting hyperpolarization of the surrounding membrane will result in the direct feedback inhibition of voltage-sensitive channels, and counteract depolarizations induced by Na^{+} influx across these glutamate receptors.

One molecular mechanism ensuring the exact placement of K_{Ca} channels with respect to other ion channels and channel modulators is through the formation of protein complexes. A number of proteins have been identified to be in close proximity to K_{Ca} channels. These include some subtypes of Ca^{2+} channels, and protein kinases/ phosphatases. Such findings raise the possibility that ion channels contain specific binding sites for other proteins such as ion channels, protein kinases, and protein phosphatases.

To determine whether K_{Ca} channels can form such modulatory protein complexes, and to characterize such binding partners, we used K_{Ca} channel fragments to screen a human brain yeast two-hybrid library. Of 171 clones identified as potentially interacting with K_{Ca} channels, 23 correspond to the -subunit of calcium calmodulin kinase II (CaMKII-). A CaMKII/K_{Ca} channel interaction was further probed using biochemical assays with GST-fusion protein constructs containing C-terminal *hslo* fragments, and either native or recombinant CaMKII or CaMKII fragments. Functional effects of CaMKII/K_{Ca} protein complexes were assayed by expressing *hslo* in *Xenopus* oocytes, and recording channel activity from inside-out macropatches. We conclude that CaMKII forms a protein complex with *hslo* Ca^{2+}-activated K^{+} channels and can modulate the activity of this ion channel.

Charalambos Kyriacou, Ph.D.
Professor of Genetics
University of Leicester
Leicester, United Kingdom
March 5, 1998

Molecular Basis For Species-Specific Behavior In *Drosophila*

Behavior is the most evolutionarily flexible phenotype and can discriminate between closely related species in the absence of any obvious morphological changes. Behavioral characters are obviously the endpoint of the expression of many genes, but differences between species may be encoded by single genes. A clear example of this comes from the study of the period (per) gene in *Drosophila*. This gene encodes a critical component of the circadian 24h clock, as well as determining the periodicity of an ultradian 60s cycle in the *D. melanogaster* male's courtship song. Transfer of the period gene from *D. simulans* to *D. melanogaster* period mutants, generates host flies which sing with the species-specific 40s love song cycle characteristic of *D. simulans* males.

The species-specificity for the lovesong cycle has furthermore been mapped to a small repetitive region within the central portion of the per coding sequence (Wheeler, et al., 1991). Consequently, in this example, a coding change, rather than a regulatory change, in a single gene determines all of the species-specificity in behavior between these two species. The per gene also determines species-specific patterns of circadian locomotor activity, in that the *D. pseudoobscura* per gene can transfer the pseudoobscura pattern to *D. melanogaster* per-mutant hosts (Petersen, et al., 1988). Chimaeric genes between these two species show that the N-terminal half of the per coding sequence encodes the species specific locomotor pattern. The corresponding experiments with locomotor patterns have also been performed with the per gene of *Musca domestica*, the housefly. Again, the per gene by itself is entirely responsible for the species-specific differences in locomotor behavior, and the sequences determining these profiles are found in the N-terminal part of the PER product (Piccin, et al., in prep).

Finally, the nonA gene in *Drosophila* also contributes species-specific information to the male lovesong. Mutations in this gene cause visual and lovesong defects, particularly in the pulse component of the song in *D. melanogaster*. Interestingly, the mutant song is reminiscent of the normal pattern of *D. virilis* songs. The *D. virilis* nonA gene was isolated and transformed into *D. melanogaster* nonA mutants. The gene fully restored the mutants' defective visual behaviour, revealing that rescue was robust, but the lovesong showed some of the characteristics of *D. virilis* pulses. Statistical analysis clearly revealed differences between *D. melanogaster* songs and those of the *virilis* nonA transformants. However, unlike per, only a small proportion of the species specific variance in the song was transferred along with *virilis* nonA. Consequently, nonA is one of probably a number of song genes that contribute to the species specific patterns in song signals. In conclusion, the molecular basis of species-specific behavior has been dissected revealing that in two phenotypes, lovesong rhythms and circadian locomotor profiles, species differences are dependent solely on the per gene. In the case of song pulses, the nonA gene is one of probably several genes which each contribute a small proportion of the species-specific behavioral variation. The latter finding conforms with the traditional view of speciation, which assumes that species differences occur by the accumulation of substitutions at many loci.

Jorge Golowasch, Ph.D.
Postdoctoral Fellow
Department of Biology and Volen
Center for Complex Systems
Brandeis University
Waltham, Massachusetts
March 6, 1998

Activity-Dependent Regulation of Conductances and Network Properties

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While plasticity is an essential property of neurons and neural circuits, the ability to maintain stable patterns of activity is equally important. Theoretical and experimental results suggest that neurons stabilize their activity by altering the number and/or characteristics of ion currents to regulate dynamically their intrinsic electrical properties. I will present experimental and modeling evidence to show that activity-dependent regulation of ionic conductances takes place in neurons from the stomatogastric ganglion of crustaceans, that it can account for the variability in the maximum conductance measured and that, by operating at the level of individual neurons, it can also stabilize network activity. Activity-dependent regulation of conductances is not a property exclusive of stomatogastric ganglion neurons and is likely to be a major mechanism regulating cellular and network activity in other preparations as well.

Alan Bawden, Ph.D.
Postdoctoral Fellow
Department of Computer Science
Brandeis University
Waltham, Massachusetts
March 6, 1998

Linear Names: Glue for Network Computing

Computer science is largely the study of naming. The addresses in memory systems, the variables in programs, the pathnames in filesystems, and the URLs printed in magazine ads are all names. Giving something a name gives us power over it, enabling us to save it for later. Or tell someone else about it.

The designers of early timesharing systems soon realized that they could do something better than simply allowing multiple users to timeslice an expensive computer—they could create an environment where people could share information by naming it and then telling each other about it. Thirty years later, a similar revolution is occurring in computer networking with the introduction of a naming mechanism—the URL—that again allows people to easily name and share information.

But this power to share things does not come for free. There is always a small amount of overhead, roughly proportional to the number of outstanding copies of the name, required to support sharing. As an example, consider a popular Web site—the more copies of the site's URL that get printed in newspapers, recited on radio, and scribbled on napkins over lunch, the more CPU power and network bandwidth will be required to support that site.

The costs of sharing are incurred by any naming mechanism, but are often small enough to be ignored when all computation takes place locally. But in a distributed computing environment, where processes and data are spread out over a network of processing elements, the costs of sharing can be particularly pernicious.

These observations lead us to investigate a restricted form of "linear" naming as a basis for distributed computing. A linear name cannot be duplicated, so it requires only a small fixed amount of overhead to implement. We have implemented network protocols to support linear names that are simple and cheap, and that allow processes and data to gracefully move from processing element to processing element. Linear names also give us a notion of "locality" that we have used to heuristically minimize network traffic. In short, linear names are a practical light-weight glue for holding a networked computation together.

Joan Rutila, Ph.D.
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Cycle is a New Circadian Rhythm Mutation in *Drosophila*

Previous behavioral screens to find genes involved in *Drosophila* circadian rhythms have identified two major players: *period* (1) and *timeless* (2). We are conducting EMS mutagenesis/behavioral screens to identify other clock genes. Our strategy is to find either suppressors or enhancers of per^{L}, on the assumption that it might be easier to uncover important clock components starting from a mutant rather than from a wild-type clock. We have identified a number of candidate mutants, which are in various stages of analysis.

Currently we are characterizing a mutant named *cycle* that has a semi-dominant phenotype. Flies that are homozygous for the cyc^{0} mutation are arhythmic, while heterozygotes have periods that are one hour longer than wild-type. Unlike the tim^{SL} mutant, a previous mutant obtained from this screen (3), this mutation is insensitive to the *per* genotype. An interesting feature of these flies is that they make very low, non-cycling levels not only of PER and TIM protein, but of *per* and *tim* mRNA as well. The defect appears to be transcriptional, since mutant flies fail to turn on *per* and *tim* transcription as shown by nuclear run-on experiments. We are now in the process of cloning this new mutation to determine if, in fact, it codes for a circadian-specific transcription factor.

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Activity-Dependent Regulation of Cortical Activity

Circuit dynamics arise from the complex interplay between synaptic connections and the intrinsic electrical properties of individual neurons. Both of these features are responsive to, and presumably regulated by, a neuron's history of activity. Here we examine how long-term activity deprivation affects the properties of neocortical neurons using electrophysiological methods. Whole-cell patch recordings were obtained from pyramidal neurons in rat visual cortical cultures. Activity was blocked in test cultures for two days prior to experiments by incubation in tetrodotoxin (TTX). After the TTX was removed, pronounced rebound phenomena were observed: ionic conductances were modulated so as to increase neuronal excitability substantially, and the strengths of excitatory synaptic connections were similarly increased. Both of these activity-dependent phenomena may be important in preserving the stability and sensitivity of neural circuits, for example during the long-lasting fluctuations in input that can accompany development and learning.

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Contextual Sensitivity in Language Comprehension

Given the high degree of ambiguity present in language, contextual sensitivity is critical to a full understanding of language. This is most evident when one examines clinical populations reported to have reduced sensitivity to context. In the domain of cognitive neuropsychology, for example, there are a number of reports that neurological damage to the right cerebral hemisphere (e.g., following stroke) results in a reduced sensitivity to contextual information in language. Additionally, others have found that schizophrenic patients also have reduced sensitivity to contextual information present in language (e.g., they consistently misinterpret double-meaning words [e.g., pen] when the surrounding sentence context biases less frequent meanings [e.g., "When the farmer bought a herd of cattle, he needed a new pen"]).

What remains unclear in characterizing the formal properties of contextual insensitivity in these populations, is a specification of the component cognitive mechanisms that produce them. In the domain of cognitive psychology and psycholinguistics, contextual sensitivity during language processing requires (at least) two important cognitive components: (1) An ability to detect contextually relevant information, and (2) an ability to inhibit contextually irrelevant information. Contextual failures following right hemisphere damage, and in schizophrenia, therefore, may not be due to failures in the internal representation of context, but may be a by-product of deficient inhibitory processing during many different levels of cognition.

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Reciprocal Regulation Phosphotyrosine and Potassium Channel Signaling

Voltage-gated potassium (Kv) channels are phosphorylated and modulated by endogenous and expressed protein tyrosine kinases. In turn, protein tyrosine phosphorylation by endogenous and expressed tyrosine kinases is reduced markedly by the expression of functional Kv channels. The levels of tyrosine kinase protein and cellular protein substrates are unaffected, consistent with a reduction in tyrosine phosphorylation that results from inhibition of protein tyrosine kinase activity. The attenuation of protein tyrosine phosphorylation is correlated with the gating properties of expressed wild type and mutant Kv channels. Furthermore, protein tyrosine phosphorylation is reduced within minutes by acute treatment with the electrogenic potassium ionophore valinomycin. Because tyrosine phosphorylation is known to influence Kv channel activity, these results suggest that reciprocal modulatory interactions occur between Kv channel and tyrosine phosphorylation signaling pathways.