Bernardo Luis Sabatini
Strange synapses – implications for biology, disease, and therapy

Affiliation:
Sabatini Lab
Howard Hughes Medical Institute
Harvard Medical School Dept of Neurobiology
Warren Alpert 347-354
200 Longwood Ave, Boston, MA 02115, USA
bernardo_sabatini@hms.harvard.edu
http://sabatini.hms.harvard.edu/
http://www.hhmi.org/scientists/bernardo-l-sabatini

Abstract
Neurons communicate via specialized contact points called synapses at which neurotransmitters are released and activate specific receptor proteins. Synaptic activity is responsible for transmitting information throughout the brain and regulation of synapses is thought to be the biological substrate underlying learning and memory formation. Here we present recent data from our laboratory on the nature of neurotransmission in the basal ganglia, a phylogenetically old and evolutionarily conserved brain area that mediates coordinated and goal-oriented motor action. In humans, dysfunction of the basal ganglia underlies many neuropsychiatric disorders such as Parkinson's, Tourette's, drug addiction, and Huntington's. We find that synapses within this region have unique cell biological and signaling properties such that they target distinct neuronal populations with different neurotransmitters. Our findings reveal an additional level of complexity in neuronal cell biology and network organization with crucial implications for the treatment of human disease.

Biography
Professor Bernardo Sabatini is based at Harvard Medical School, and is also a Howard Hughes Medical Institute (HHMI) Investigator. His laboratory seeks to uncover the mechanisms of synapse and circuit plasticity that permit new behaviors to be learned and refined. They are interested in the developmental changes that occur after birth that make learning possible as well as in the circuit changes that are triggered by the process of learning. Lastly, they examine how perturbations of these processes contribute to human neuropsychiatric disorders such as Tuberous Sclerosis Complex and Parkinson's disease.

Organizers
Linda H Bergersen and Jon Storm-Mathisen in cooperation with the University of Oslo, the Nansen Neuroscience Network (NNN), and the Norwegian Academy of Science and Letters (DNVA).

* Nansen as neuroscientist: see notes at http://www.dnva.no/kalender/vis.html?tid=48780
Previous NNL: see below
**Amy FT Arnsten**  
*Molecular events in Nansen’s "Dotted Substance": Intracellular mechanisms governing higher cognitive network connections*

**Affiliation:**  
Amy FT Arnsten, PhD  
Professor of Neurobiology and of Psychology  
Founding Member, Kavli Institute of Neuroscience  
Yale University, New Haven, CT, USA.  
amy.arnsten@yale.edu  
http://medicine.yale.edu/lab/arnsten/

**Abstract**  
The highly evolved, primate dorsolateral prefrontal association cortex (PFC) generates the mental representations that are the foundation of abstract thought. The PFC can maintain information in the absence of sensory stimulation using networks of pyramidal cells that excite each other through NMDA type glutamate receptors at synapses on dendritic spines, constituents of the “dotted substance” first noted by Nansen. The numbers and complexity of layer III pyramidal cells expand greatly in primate evolution, and these neurons are gravely afflicted in both schizophrenia and Alzheimer’s Disease. We have discovered that the strength of these PFC network connections is dynamically altered by the arousal systems, likely contributing to changes in conscious state and in higher mental abilities. For example, cholinergic stimulation of nicotinic alpha7 receptors in the synapse is needed for NMDA receptors to open and networks to connect when we are awake. The catecholamines control feedforward calcium-cAMP signaling events in the spine that can open or close potassium channels, rapidly weakening or strengthening connections, respectively. These molecular events help to shape the contents of working memory, and determine the strength of our higher cognitive abilities. We hypothesize that other association cortices, e.g. the entorhinal cortex, may also have mechanisms for dynamic regulation of network inputs. In contrast, the neuropil in the primary visual cortex reveals a fundamentally different landscape. In these more faithful connections, cAMP appears to have opposite effects compared to those in the PFC, e.g. strengthening connections by increasing glutamate release instead of weakening network inputs. Thus, the arousal systems can orchestrate brain circuits, e.g. enhancing sensory processing and weakening higher cognition during stress exposure. Importantly, many of the molecules that rein in the stress response, such as the phosphodiesterase PDE4A and its anchoring protein DISC1 (Disrupted In Schizophrenia), are genetically linked to schizophrenia. We have also found that PDE4A expression is reduced with advancing age, leading to the hyperphosphorylation of tau in the higher cortical circuits that degenerate in Alzheimer’s disease. Thus, understanding the unique molecular regulation of the association cortices may help us understand the fragility of our higher cognitive abilities, and give rational strategies for the treatment of cognitive disorders.

**Biography**  
Dr. Amy F.T. Arnsten is Professor of Neurobiology at the Yale University School of Medicine and a founding member of the Kavli Institute of Neuroscience at Yale. She received her B.A. with Honors in Neuroscience from Brown University in 1976, and her Ph.D. in Neuroscience from the University of California, San Diego in 1981. Following her doctoral studies, Dr. Arnsten performed post-doctoral research with Dr. Susan Iversen at the University of Cambridge in England and then with Dr. Patricia Goldman-Rakic at Yale University. Dr. Arnsten’s research focuses on the highly evolved primate prefrontal cortex, elucidating the unique molecular mechanisms that dynamically alter the strength of network connections, shaping the contents of thought and coordinating state of arousal with cognitive abilities. Her lab has uncovered molecular events that take the prefrontal cortex “off-line” during uncontrollable stress, and has found that genetic and/or environmental insults in this process may contribute to cognitive impairment in mental illness and in aging. Arnsten’s research has led to new treatments for prefrontal deficits in patients: 1) guanfacine (IntunivTM), for the treatment of Attention Deficit Hyperactivity Disorder and a variety of prefrontal cortical disorders; and 2) prazosin, for the treatment of Post-Traumatic Stress Disorder.

**Organizers**  
Linda H Bergersen and Jon Storm-Mathisen in cooperation with the University of Oslo, the Nansen Neuroscience Network (NNN), and the Norwegian Academy of Science and Letters (DNVA).
The Nansen Neuroscience Lecture 2013
http://english.dnva.no/
http://www.dnva.no/

When: Thursday 10 October 2013, 11:15 – 12:00
Where: The Norwegian Academy of Science and Letters – DNVA, Drammensv 78, 0271 Oslo
Why: The Nansen Neuroscience Lectures (NNL) are organized on Fridtjof Nansen’s birthday to commemorate Nansen’s fundamental contribution to neuroscience*. The NNL are given by speakers selected from the top tier of international neuroscience research.

Jeff W. Lichtman
"Connectomics: What, How, and Why?"

Affiliation:
Department of Molecular and Cellular Biology
Harvard University
Cambridge MA 02138
Email: jeff@mcb.harvard.edu
http://www.hms.harvard.edu/dms/neuroscience/fac/lichtman.php

Abstract:
Connectional maps of the brain may have value in developing models of both how the brain works and how it fails when subsets of neurons or synapses are missing or disconnected. Such maps might also provide detailed information about how brain circuits develop and age. I am eager to obtain such maps in neonatal animals because of a longstanding interest in the ways neuromuscular circuitry is modified during early postnatal life as axonal input to muscle fibers is pruned. Work in my laboratory has focused on obtaining complete wiring diagrams (“connectomes”) of the projections of motor neuron axons in young and adult muscles. Each data set is large and typically made up of hundreds of confocal microscopy stacks of images which tile the 3-dimensional volume of a muscle. As a first step to analyze these data sets we developed computer assisted segmentation approaches and to make this task easier, have developed second generation “Brainbow” transgenic mice that in essence segment each axon by a unique fluorescent spectral hue. Once the axons are segmented, we have been able to graph the connectivity matrices that result. This effort has led to new insights into the developmental processes that help the mammalian nervous system mold itself based on experience. Analysis of these complete muscle connectomes show a striking single axis gradient of connectivity that we think is related to the ordered ranking of neural activity in axons (the “size principle” of Henneman). In brain however, as opposed to muscle, the high density of neuropil is overwhelming, which has precluded using the confocal optical approaches that have worked in the peripheral nervous system because there are too many neural processes in each optical section. We have thus developed a lossless automated physical sectioning strategy that generates thousands of ultra thin (~25 nm) sections on a firm plastic tape. We have developed a thin-section scanning electron microscopy approach to visualize these sections at 3 nm lateral resolution. This method makes large scale serial microscopic analysis of brain volumes more routine. We are now focused on developing an automated pipeline to trace out neural circuits in brains using this technique.

Biography:
Jeff Lichtman is Jeremy R. Knowles Professor of Molecular and Cellular Biology and Santiago Ramón y Cajal Professor of Arts and Sciences at Harvard University. He received an AB from Bowdoin (1973), and an M.D. and Ph.D. from Washington University (1980) where he worked for 30 years before moving to Cambridge in 2004. He is a member of the newly established Center for Brain Science. Lichtman’s research interest revolves around the question of how mammalian brain circuits are physically altered by experiences, especially in early life. He has focused on the dramatic re-wiring of neural connections that takes place in early postnatal development when animals are doing most of their learning. This work has required development of techniques such as “Brainbow” transgenic mice to visualize neural connections and monitor how they are altered over time. Recently his efforts have focused on developing new electron microscopy methods to map the entire wiring diagram of the developing and adult brain. This “connectomics” approach has as one of its aims uncovering the ways information is stored in neural networks.

Organizers:
Linda H Bergersen and Jon Storm-Mathisen in cooperation with the University of Oslo, the Nansen Neuroscience Network (NNN), and the Norwegian Academy of Science and Letters (DNVA).

* Nansen as neuroscientist: see notes at http://www.dnva.no/kalender/vis.html?tid=48780
Previous NNL: see below
The Nansen Neuroscience Lectures 2012
http://english.dnva.no/
http://www.dnva.no/

When: Wednesday 10 October 2012, 12:15 – 14:00
Where: The Norwegian Academy of Science and Letters – DNVA, Drammensv 78, 0271 Oslo
Why: The Nansen Neuroscience Lectures (NNL) are organized on Fridtjof Nansen’s birthday to commemorate Nansen’s fundamental contribution to neuroscience*. The NNL are given by speakers selected from the top tier of international neuroscience research.

Admission: Open to public, no charge

A. David Smith
Slowing progression in Alzheimer’s disease by lowering homocysteine – evidence from neuroimaging

Semir Zeki
The neurobiology of beauty

Affiliations of speakers:

A. David Smith, FMedSci
Professor emeritus of Pharmacology
University of Oxford
Founding Director of Oxford Project to Investigate Memory and Ageing (OPTIMA)
http://www.medsci.ox.ac.uk/optima
Hon. Assoc. Director MRC Anatomical Neuropharmacology Unit
http://www.mrc.ox.ac.uk/

Semir Zeki, FRS, FMedSci
Professor of Neuroaesthetics
(having previously held the Chair of Neurobiology)
University College London
http://www.vislab.ucl.ac.uk/
http://profzeki.blogspot.com/

Abstracts:

A. David Smith
Slowing progression in Alzheimer’s disease by lowering homocysteine – evidence from neuroimaging
Alzheimer’s disease (AD) progresses from an asymptomatic stage, through mild cognitive impairment (MCI), to eventual dementia. One therapeutic approach is to modify risk factors in the early stages. Raised plasma total homocysteine is a risk factor for AD and can be lowered by B vitamins (folate, vitamins B12 and B6). In the 2-year VITACOG trial we found that B vitamins slowed cognitive and clinical decline in those with MCI who had high baseline homocysteine. The B vitamins also markedly slowed atrophy in those regions of the brain that show loss of tissue in AD.

Semir Zeki
The Neurobiology of Beauty
The lecture will be a neurobiological dissection of one of the most famous definitions of beauty, given by Edmund Burke in A Philosophical Enquiry into the Origin of our Ideas of the Sublime and Beautiful (1757): “Beauty is, for the greater part, some quality in bodies acting mechanically upon the human mind by the intervention of the senses”. I will examine, in light of experimental evidence, the four pillars of this definition: the abstract nature of beauty (as is implied in the definition), the human mind in the experience of beauty, the quality in bodies (that arouse the sense of beauty) and the neural nature of the intervention by the senses.

Organizers:
Linda H Bergersen and Jon Storm-Mathisen in cooperation with the Centre for Molecular Biology and Neuroscience (CMBN) at the University of Oslo, the Nansen Neuroscience Network (NNN), and the Norwegian Academy of Science and Letters (DNVA).

* Nansen as neuroscientist: see notes at http://www.dnva.no/kalender/vis.html?tid=48780
Previous NNL: see below
The Nansen Neuroscience Lectures

The Nansen Neuroscience Lectures (NNL) were organized for the first time on 11 October 2010 (in conjunction with Fridtjof Nansen's birthday 10 October) by the Centre for Molecular Biology and Neuroscience (CMBN) in cooperation with the Nansen Neuroscience Network (NNN) and the Norwegian Academy of Science and Letters (DNVA).

The program of the ‘NNL101010’ is shown below.

In the Nansen jubilee year 2011, the NNL were replaced by the Fridtjof Nansen Science Symposium, neuroscience part, 28 April 2011 http://www.dnva.no/kalender/vis.html?tid=48780

"Nansen Neuroscience Lectures 101010"

Where: Nye auditorium 13, Domus medica, Sognsvannsv 9, University of Oslo
When: Monday 11th October 2010, at 11:00-13:45
http://www.cmbn.no/events-2010.html

11:00-11:15
Jon Storm-Mathisen, Professor, Centre for Molecular Biology and Neuroscience, University of Oslo, and Stein Lorentzen-Lund, Project Director, Nansen Neuroscience Network:
"Nansen Neuroscience Network - innovation 123 years after the nascence of Norwegian neuroscience" (Nansen's thesis published 1887)

11:15-12:00
Albert Gjedde, Professor, Department of Neuroscience and Pharmacology, University of Copenhagen:
"PET studies of oxygen delivery to brain tissue in humans in vivo: effects of aging, exertion and disease"
Short introduction by Johanne Egge Rinholm, PhD, UiO

12:00-12:15 Coffee, fruits, refreshments

12:15-13:00
Kenneth Hugdahl, Professor, Department of Biological and Medical Psychology, University of Bergen:
"Functional neuroimaging: promises and challenges -- unravelling the neuroscience of auditory hallucinations in schizophrenia"
Short introduction by Cecilie Morland, PhD student, UiO

12:00-13:45
May-Britt Moser, Professor, The Kavli Institute for Systems Neuroscience & Centre for the Biology of Memory, NTNU, Trondheim:
"How does the brain navigate in space"
Short introduction by Lasse Ormel, PhD student, UiO

13:45 End of lectures

The Nansen Neuroscience Lectures 101010 are organized in conjunction with Fridtjof Nansen's birthday by the Centre for Molecular Biology and Neuroscience (CMBN) of the University of Oslo in cooperation with the Nansen Neuroscience Network (NNN) and the Norwegian Academy of Science and Letters (DNVA).

Organizing committee: Linda H Bergersen, Jon Storm-Mathisen

The inaugural Nansen Neuroscience Lectures speakers:
Albert Gjedde,
Kenneth Hugdahl,
May-Britt Moser