

Models of Synaptic Plasticity: Potential Roles in Development, Cognition, and Disease

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Dan Madison, PhD

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Talk Summary:

Synaptic States: Our published data, showed that activity dependent synaptic plasticity exhibits a mechanistic state-dependence. When undergoing LTP, LTD, depotentiation, silence synapse awakening, and similar plasticity, the synaptic strength changes occur by the common final path of the regulation of AMPA receptor concentration in the postsynaptic membrane. But the mechanisms by which these receptors are trafficked into and out of the membrane change, depending on what plasticity the synapse has undergone. So far, we have defined 7 and possibly 8 distinct mechanistic plasticity states of the synapse. As an example of what I mean by 'states', the strength of a naive active synapse can be suppressed by low-frequency synaptic activity via activation of the NMDA receptor. But if you first potentiate the synapse, the same low-frequency activity still depresses it's strength, but now through the activation of an mGluR receptor (and the NMDAR sensitivity is removed). So naive-active synapses and potentiated synapses can both undergo similar plasticity, but the underlying mechanisms are different. In a similar vein, naive-active synapses and silent synapses can both be potentiated by high-frequency activity that adds AMPARs to the postsynaptic mechanism, but these AMPARs come from different sources and are regulated by different underlying mechanisms. In our more recent unpublished data, we have found that a major factor underlying these states is the insertion or removal of AMPARs having different subunit composition. The main thrust of the talk is to use the rules that states provide to understand the mechanisms underlying synaptic plasticity. By doing this, we have just recently completed a fairly comprehensive model to explain how the trafficking of AMPARs with different subunit compositions underlies much of the state-dependence of plasticity.

R. Douglas Fields, PhD
"Synaptic Plasticity: Venturing Beyond the Cleft"

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Talk Summary:

The once hotly debated issue of the relative importance of the presynaptic versus postsynaptic membrane in regulating synaptic plasticity fueled years of productive research, but now the field is venturing beyond the synaptic cleft. Signaling to the nucleus and cell-cell interactions of many types are important in regulating synaptic strength. Hebb's postulate that the coincident firing of neurons is the essential trigger for learning implies the importance of action potentials, not simply synaptic potentials, in regulating plasticity. Different intracellular signaling pathways are activated by action potentials and synaptic potentials, and our research suggests that gene transcription necessary for consolidating early into late-phase LTP does not require synaptic signaling to the nucleus, but rather somatic action potentials. Cell-cell interactions with non-neuronal cells, astrocytes, also regulate plasticity of synapses, but less-well appreciated is the transmission of impulses through axons, which is regulated in part by myelinating glia. The conduction velocity and synchrony of impulses are critical in information processing and synaptic transmission. New research suggests that myelinating glia sense impulse activity in axons and regulate the process of myelination. This new aspect of plasticity encompasses white matter changes in addition to the grey matter changes in learning, and the molecular mechanisms for activity-dependent communication between axons and myelinating glia are being identified. The activity-dependent communication involves extracellular ATP and cytokines, which are relatively less well-explored in LTP research. Our research finds impaired LTP in mice lacking the gene for the cytokine LIF, and cell-cell interactions mediated by LIF and ATP are important in activity-dependent regulation of nervous system development and myelination.

Alfredo Kirkwood, PhD
"Neuromodulation of Synaptic Plasticity"

Associate Professor
Zanvyl Krieger Mind/Brain Institute
Johns Hopkins University
<http://neuroscience.jhu.edu/AlfredoKirkwood.php>

Talk Summary:

Sensory experience can shape the connectivity of the cerebral cortex during its maturation in infants, and also during learning in adults. These neural modifications depend critically on neuromodulators conveying information of the behavioral state of the organism such that passive experience does not leave permanent traces on cortical connectivity. Research on the mechanisms of neural plasticity indicated that the connection between two neurons can be either strengthened or weakened depending on their patterns of neural activity, particularly on their "timing" relationships. Typically, synapses become either stronger or weaker depending on whether pre- or postsynaptic activity occurs first. I will discuss evidence indicating that the "timing-dependence" rules of synaptic modification are not fixed, but emerge from the interactions of neuromodulators. As one important consequence, a given pattern of pre- and postsynaptic activity can modify synapses in opposite directions depending on the neuromodulators present.

Eric Klann, PhD
"Altered Synaptic Plasticity and Behavior in Mouse Models of
Mental Retardation"

Professor of Neuroscience
Center for Neuroscience
New York University
<http://www.cns.nyu.edu/corefaculty/Klann.php>

Talk Summary:

Genetic deletion and/or mutations of several translation repressor proteins, including fragile X mental retardation protein (FMRP) and tuberous sclerosis complex 1 and 2 (TSC1/2), are associated with human mental retardation. Because de novo protein synthesis is one of the hallmarks of long-lasting synaptic plasticity and long-term memory, genetically engineered mouse models that lack translational control proteins have the potential to provide insight into the molecular and cellular basis of mental retardation and autism. In this presentation, synaptic plasticity and behavioral studies of mice that lack specific translation factors and translation regulatory proteins, including FMRP, will be discussed. These studies have revealed interesting links between the biochemical activities of translation factors, synaptic plasticity, and behavior.

Per Svenningsson, MD, PhD

"Involvement of 5-HT_{1B} Receptors and p11 in Depression and Parkinson's Disease"

Group Leader

Department of Physiology and Pharmacology

Karolinska Institute, Stockholm

<http://ki.se/ki/jsp/polopoly.jsp?d=9791&l=en>

Talk Summary:

Christina Vargas-Irwin, PhD

"Individual Differences in Addictive Behavior: A Process Approach"

Research Associate Professor

Department of Pharmacy

Virginia Commonwealth University

<http://www.pharmacy.vcu.edu/pharmacy/facdetail.aspx?id=784>

Talk Summary:

The progression towards addictive behavior has been described as involving the transition through several stages, beginning with the initial contact with the drug, followed by its regular use, which, in turn may finally result in substance dependence, or addiction. This sequence is not deterministic, since in humans, most drug users don't become drug dependent, and many factors, such as availability, genetics, history of drug use, stress, and life events contribute to the final outcome. Research in this area has traditionally approached individual differences in addictive behavior from a static trait centered perspective, which is inherently silent about behavioral dynamics and non-specific about gene-environment interactions. We pursue here a process-oriented approach to the study of addictive behavior, focused on the reward and hedonic properties of drugs. From this perspective, individual differences are conceived not as static traits, but rather as dynamic parametric differences in common behavioral processes. This approach is illustrated with examples from our own research and its implications to the links between addictive behavior and synaptic plasticity are highlighted.