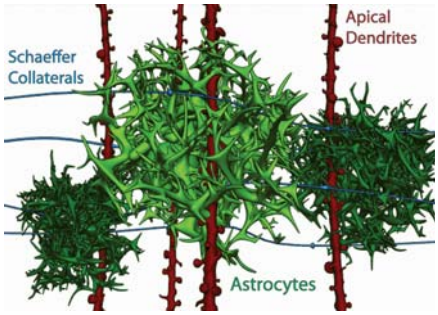
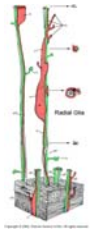
Structural plasticity of neuron-glial interactions at excitatory synapses



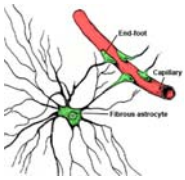
Centre for Research in Neuroscience
The Research Institute of the McGill University Health Centre
Montreal General Hospital

Roles of Glia in CNS Development and Function

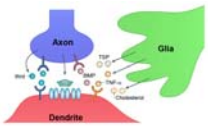


Neural Migration

Myelination

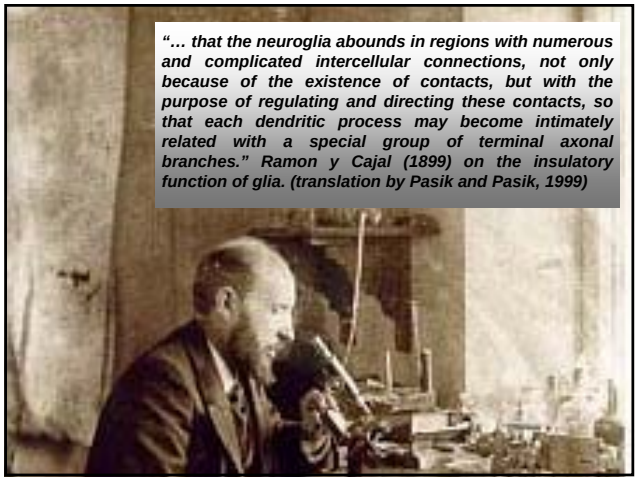


Blood Brain Barrier



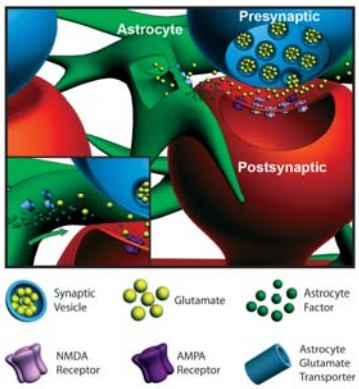
Li and Sheng, 2003.

Synaptic Development/Function



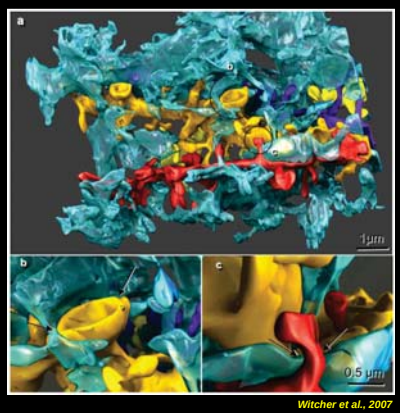
"… that the neuroglia abounds in regions with numerous and complicated intercellular connections, not only because of the existence of contacts, but with the purpose of regulating and directing these contacts, so that each dendritic process may become intimately related with a special group of terminal axonal branches." Ramon y Cajal (1899) on the insulatory function of glia. (translation by Pasik and Pasik, 1999)

Astrocytes and Synaptic Function



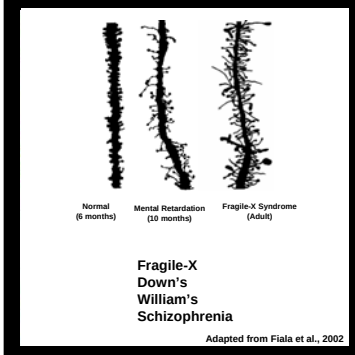
- Ion homeostasis (i.e. K+ uptake)
- Neurotransmitter re-uptake (GLT-1/EAAT-2; GLAST/EAAT-1)
- Respond to neural activity with calcium transients
- Vesicular-mediated release of (ATP, glutamate, D-serine)
- Heterosynaptic plasticity
- **Structural modifications**

Complex Association of Astrocytes and Synapses in the Hippocampus



Witcher et al., 2007

Structural Plasticity in the CNS- Dendritic Spines



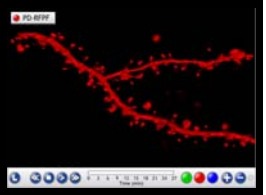
Fragile-X
Down's
William's
Schizophrenia

Adapted from Fiala et al., 2002

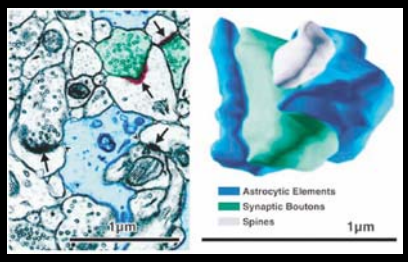
Biochemical Compartments

Activity-Dependent Restructuring
- **modifications to synaptic efficacy**
- **synaptic reorganization?**

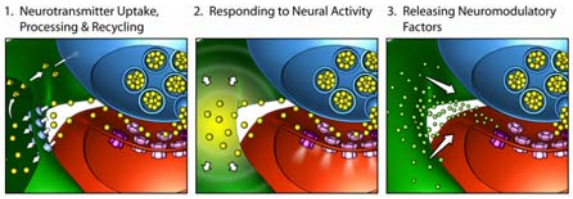
Altered in Disease?



Complexity of astrocyte-synapse interactions



(Auld and Robitaille, 2003; Ventura and Harris, 1999)

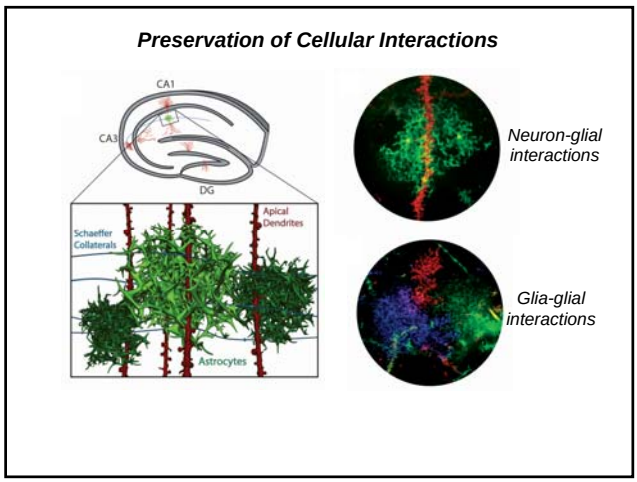


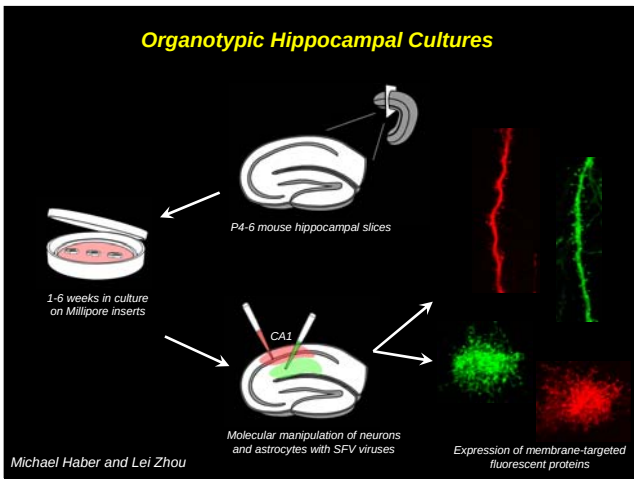
Is there structural plasticity of neuron-glial complexes at excitatory synapses?

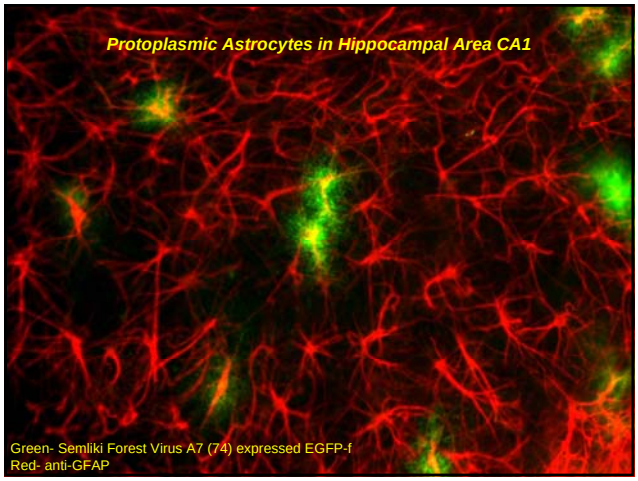
1) Do astrocytes exhibit structural remodeling events over short time frames?

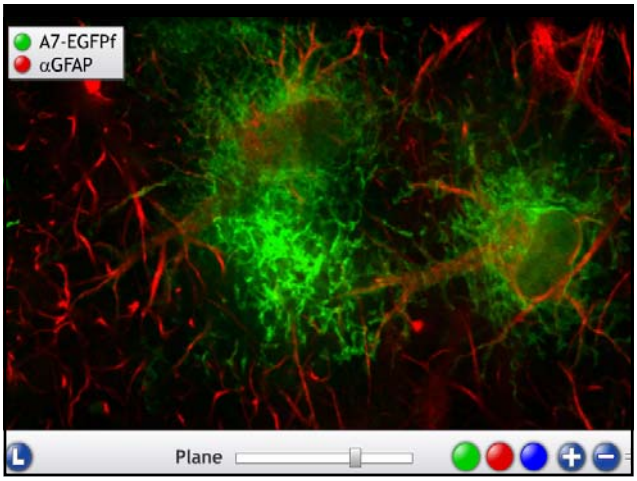
2) What is the relationship of astrocyte to dendritic spine dynamics?

3) What are the properties of neuron-glial structural plasticity?

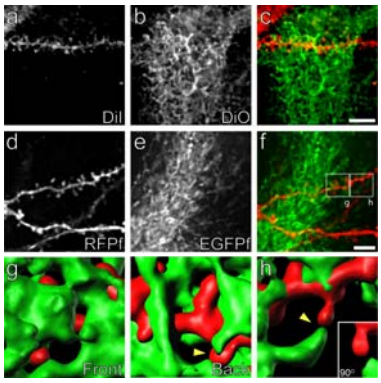

Preservation of Cellular Interactions
CA1
CA3
DG
Schaeffer Collaterals
Apical Dendrites
Astrocytes
Neuron-glial interactions
Glia-glial interactions


Organotypic Hippocampal Cultures
P4-6 mouse hippocampal slices
1-6 weeks in culture on Millipore inserts
CA1
Molecular manipulation of neurons and astrocytes with SFV viruses
Expression of membrane-targeted fluorescent proteins
Michael Haber and Lei Zhou

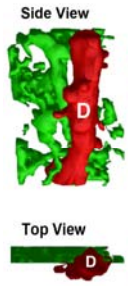

Protoplasmic Astrocytes in Hippocampal Area CA1
Green- Semliki Forest Virus A7 (74) expressed EGFP-f
Red- anti-GFAP


A7-EGFPf
αGFAP
Plane

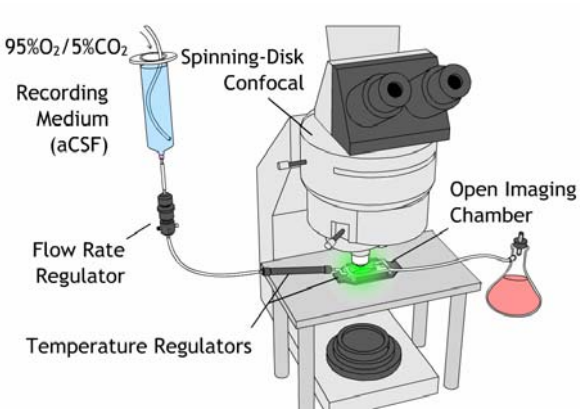
Complex Neuron-Glial Interactions



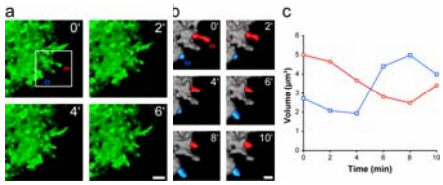
Michael Haber



1) Do astrocytes exhibit structural remodeling events over short time frames?

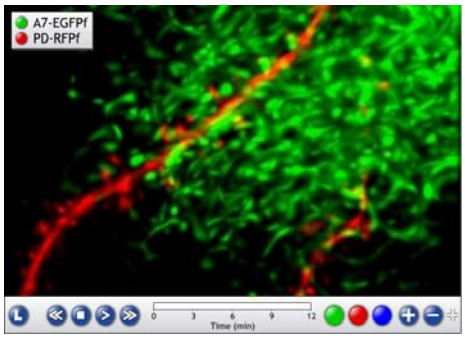


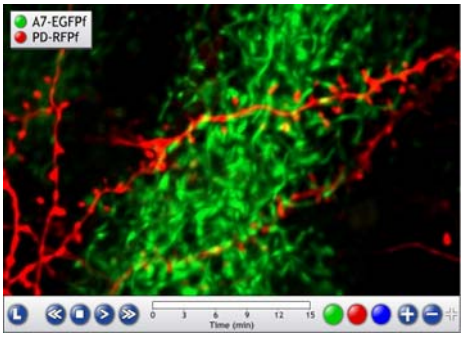
Astrocytes show dynamic structural changes in Area CA1 of the hippocampus

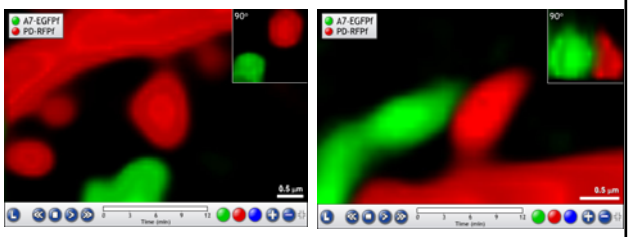


Michael Haber

Neuron-Glial Dynamics in the Hippocampus

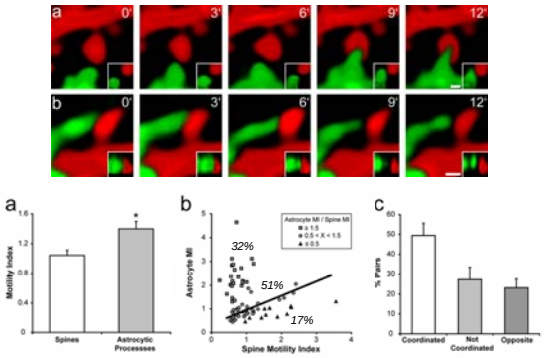






2) What is the relationship of astrocyte to dendritic spine dynamics?

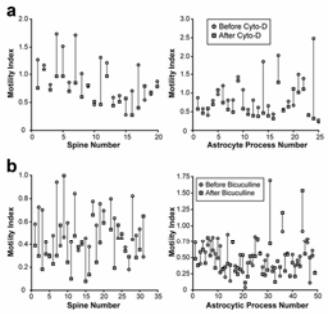
Astrocyte vs. Dendritic Spine Dynamics



3) Properties of Astrocyte and Dendritic Spine Dynamics

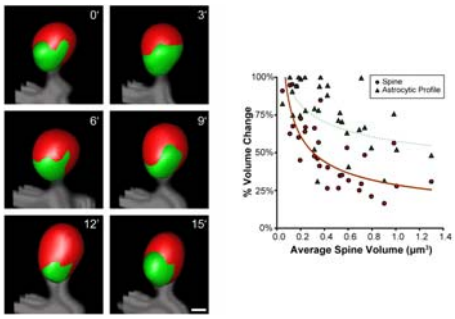
Cytochalasin-D

Bicuculline-
$GABA_A$ Receptor Blocker

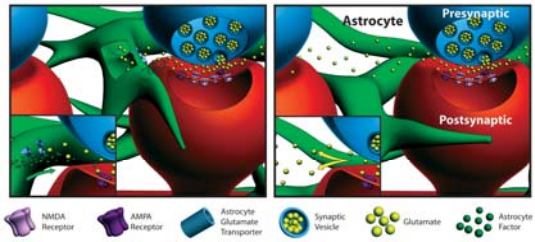


- *Remodeling is likely actin-based*
- *Activity differentially affects the motility of spines and astrocytic processes*

Dynamic Changes in Astrocytic Coverage of Spines

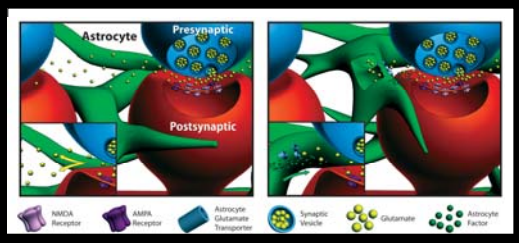


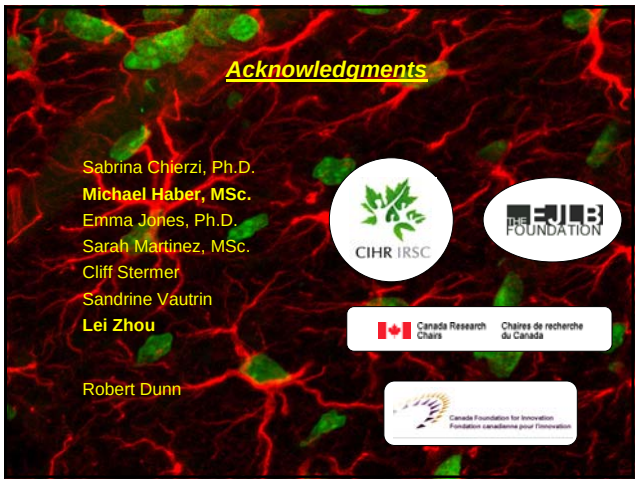
Model for the Modulation of Synaptic Function by Astrocyte Dynamics



Conclusions

- Astrocytes exhibit wide-spread structural modifications over seconds to minutes
- Complex morphological interactions take place between astrocytic processes and dendritic spines (actin-based, differential effects of activity, influenced by spine size)
- Astrocyte-spine remodeling may regulate the physiological properties excitatory synapses through local modifications to the synaptic environment
  > Implications for synaptic plasticity, cognition, neuropathological conditions




Acknowledgments
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