Memory is Malleable

- Behavior
- Decisions
- Goals
- Ideas
- Skills

How are memories made and stored in the brain?
EXERCISE

SYNAPTIC PLASTICITY: 
the most accepted mechanism for memory storage

THE SEARCH FOR NEW MECHANISMS
An Exercise in Learning and Making Connections
What did you learn?

• Most of the people don’t remember all colors for circle and star
• Usually people remember that square came always with orange color

How can an individual recall that the square was orange?
The nature of memory is not set in stone…

Wikipedia ➔ Dynamic memory

Recording tape ➔ Static memory
An Example of Dynamic Memory

“About how fast were the cars going when they ______ each other?”

<table>
<thead>
<tr>
<th>Verb</th>
<th>Mean Speed Estimate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smashed</td>
<td>40.5</td>
</tr>
<tr>
<td>Collided</td>
<td>39.3</td>
</tr>
<tr>
<td>Bumped</td>
<td>38.1</td>
</tr>
<tr>
<td>Hit</td>
<td>34.0</td>
</tr>
<tr>
<td>Contacted</td>
<td>31.8</td>
</tr>
</tbody>
</table>
An Example of Dynamic Memory

No Broken Glass!

An Example of Dynamic Memory

One week later…

“Did you observed any broken glass?”

<table>
<thead>
<tr>
<th>Verb Condition</th>
<th>Response</th>
<th>Smashed</th>
<th>Hit</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes</td>
<td>16</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>34</td>
<td>43</td>
<td>44</td>
</tr>
</tbody>
</table>

The Nature of Memory

(1) Memories can be stored…

(2) Memory is dynamic…

What is the basis for these characteristics of memory?
The Ground-Breaking Investigations

Late 19th century: ~100 billion neurons

Long Term Potentiation: Hebbian Theory

LTP is a long-lasting increase in the efficiency of synaptic transmission between neurons that is believed to be the cellular basis of memory.

First Experiment Observation of Long Term Potentiation

Terje Lømo first observed LTP in 1966.

Lomo T. Phil. Trans. R. Soc. Lond. B. 2003. 13,
Different Aspects of LTP

- Biochemical
- Structural
Mathematical Model of a Neuron

\[ x = \sum_{i=1}^{N} W_i I_i \]

Inputs: I₁, I₂, I₃, I₄

Outputs: S

Dendrite
Axon
Soma (Cell Body)
Synapses
Neural Networks

1. Train with input/output data - adjust weighting functions and step functions.
2. Receive output for new input data set.
A Closer Look at Synapse

- Neurotransmitters
- Exocytosis of neurotransmitters
- Ion Channels
- Cellular transport of vesicles
- Cell morphology
- Gene regulation

A Look Back at the Exercise
Wikipedia vs. Recording Tape

- Smashed
- Contacted
- Bumped
- Broken Glass
Memory and Biological Body

Biochemical \hspace{1cm} \leftrightarrow \hspace{1cm} \text{Structural}
Molecular Turnover

[Diagram of molecular turnover and memory formation from Francis Crick]

Crick F. *Nature*, 1985, 313, 21
Two Copies for Memory

Crick F. *Nature*, 1985, 313, 21
Proposed Mechanism for Mnemogenic Reaction

Stimulus $\rightarrow$ K$_2$

K$_1$ $\rightarrow$ ATP $\leftarrow$ Phosphatase

K$_1^*$ $\rightarrow$ Neuronal Function

Enzymatic Activity in Mnemogenic Reaction

Threshold in Mnemogenic Reaction

HIGH ENERGY CONSUMPTION

A More Efficient Approach

Requirements for Memory Storage

- Memory is stored as a structural change of neurons
- Synaptic strength is key component of memory storage
- A switch function is necessary to store memory
The Search for a Memory Molecule

Protein Kinase Family:

★ CaMKII (Calcium/calmodulin-dependent protein Kinase II)
★ cAMP- dependent protein Kinase
★ ERK (Extracellular signal-regulated Kinase)
★ cdk5 (cyclin-dependent Kinase 5)

Griffith L. j. Neurosci. 2004, 24, 8391-8393
Kinases are the Candidate Molecule

- ~500 Kinase are identified in the human genome
- 30% of proteins are believed to be modified by phosphorylation
- Their function is believed to be regulatory machinery of cells to control other proteins activity

Manning G et. al. Science, 2002, 298, 1912
CaMKII (Calcium/calmodulin-dependent protein Kinase II)

- Alpha-beta-gamma-delta are 4 isoforms of CaMKII.
- Alpha and beta are expressed exclusively in nervous system.
- 1% of protein content of brain.

Experimental Observations for the Significance of CaMKII


Mutant Mouse lacking alpha-CaMKII
CaM Kinase

Griffith L. *j. Neurosci.* 2004, 24, 8391-8393
Monomer of CaM Kinase II

- **Ca\(^{2+}\)/Calmodulin**
- **Active Site**
- **Substrate**
- **Thr286**
- **Inactive CaMKII No Memory**
- **Ca\(^{2+}\)/Calmodulin dependent Activation of CaMKII**
- **Ca\(^{2+}\)/Calmodulin independent Activation of CaMKII**

Dimer of CaM Kinase II

Levels of CaM Kinase Activation

0.1-0.2 s  
Active state

Several minutes  
Active state

Long-Term Persistent Activation

Last for very long time

Low Frequency Activation

High Frequency Activation

Simulation of CaM Kinase II

\[ W_I \leftrightarrow W_B \rightarrow W_P \leftrightarrow W_T \leftrightarrow W_A \]

<table>
<thead>
<tr>
<th>State</th>
<th>Symbol</th>
<th>Ligand</th>
<th>Phosphorylation at Thr^{286}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inactive</td>
<td>( W_I )</td>
<td>-</td>
<td>No</td>
</tr>
<tr>
<td>Bound</td>
<td>( W_B )</td>
<td>4Ca^{2+}- CaM</td>
<td>No</td>
</tr>
<tr>
<td>Phosphorylated</td>
<td>( W_P )</td>
<td>4Ca^{2+}- CaM</td>
<td>Yes</td>
</tr>
<tr>
<td>Trapped</td>
<td>( W_T )</td>
<td>CaM</td>
<td>Yes</td>
</tr>
<tr>
<td>Autonomous</td>
<td>( W_A )</td>
<td>-</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Dupont G. et.al. *Cell Calcium*, 2003, 34, 485-497
Phosphorylation of Thr$_{286}$

Neuron “Protein Switches”

- Neurons have a protein machinery that acts like a switch

- This switch will turn off for less frequent inputs but for inputs with high repetition will stay on always

But, how this switch can change the strength of synapse?
CaM Kinase’s Substrates

Increase NMDA receptor and Binds to Membrane

NMDA Receptor

CaM Kinase II

AMP A Receptor
Enhance Channel function by phosphorylation

CREB (Transcription Factor)
Controls Gene Regulation

CaM Kinase’s Substrates

Voltage sensitive Ca\textsuperscript{2+} channel

Ligand gated receptor channel

Ca\textsuperscript{2+}

Ca\textsuperscript{2+}

Ca\textsuperscript{2+}/CaM

CaM kinase II

Gene expression

Protein phosphorylation

Regulation of nerve functions

Neurotransmitter synthesis
Neurotransmitter release
Ion channel and receptor function
Calcium homeostasis
Cytoskeletal function
Gene expression
Synaptic plasticity
Learning and memory

Differ. signal
Binding protein
Looking for New Mechanisms of Memory Formation

A recent proposal…
Ingredients?
Ingredients 1: Metals

<table>
<thead>
<tr>
<th>Metal</th>
<th>Levels</th>
<th>Behavioral Changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aluminum (Al)</td>
<td>Toxic</td>
<td>Memory loss, altered behavior, confusion, disorientation (see Alzheimer's disorder)</td>
</tr>
<tr>
<td>Calcium (Ca)</td>
<td>Deficiency</td>
<td>Severe intellectual changes, mental retardation, poor memory</td>
</tr>
<tr>
<td>Copper (Cu)</td>
<td>Tissue overload</td>
<td>Wilson’s disease; psychiatric manifestations</td>
</tr>
<tr>
<td>Iron (Fe)</td>
<td>Deficiency</td>
<td>Poor memory; dietary iron supplementation correlated with improvement of memory</td>
</tr>
<tr>
<td>Iron (Fe)</td>
<td>Tissue overload</td>
<td>Thalassemia; anxiety, depression, psychiatric disfunctions</td>
</tr>
<tr>
<td>Lead (Pb)</td>
<td>Toxic</td>
<td>Mental deterioration, aggressive, poor memory, lower IQ</td>
</tr>
<tr>
<td>Lithium (Li)</td>
<td>Therapy</td>
<td>Memory improvement, mental slowness (variable reports)</td>
</tr>
<tr>
<td>Magnesium (Mg)</td>
<td>Toxic</td>
<td>Mental confusion, impaired memory</td>
</tr>
<tr>
<td>Mercury (Hg)</td>
<td>Toxic</td>
<td>Loss of memory, behavioral changes</td>
</tr>
<tr>
<td>Thorium (Th)</td>
<td>Toxic</td>
<td>Mental confusion</td>
</tr>
<tr>
<td>Zinc (Zn)</td>
<td>Deficiency</td>
<td>Loss of memory</td>
</tr>
</tbody>
</table>

Ingredients 2: Extracellular Space (nECM)

Ingredient 2: Extracellular Space (nECM)

Hyaluronic Acid (HA)
Proteoglycans
Chondroitin Sulfates (Chon)
Heparan Sulfates (Hep) and Keratan Sulfate

Ingredient 2: Extracellular Space (nECM)

Chondroitinase ABC: removes chondroitin
+/+: wild type
-/-: mutant lacking Tenascin-R

Ingredient 3: The Neuron

*But more precisely the neuron membrane...*

Tripartite Mechanism

\[ n\text{ECM} + M^{+V}(H_2O)_4 \leftrightarrow [n\text{ECM}: M^{+V}] + 2H_2O \]

\( v = \text{valance range 1 to 3} \)

cuinfo
pinned, immobile complex


Short and long term memory

\[ \text{nECM} + \text{M}^{+1} \rightleftharpoons [\text{nECM: M}^{+1}] \rightleftharpoons [\text{nECM: M}^{+>>2}] \]

- free
- cuinfo\(^1\)
  - Unstable
- cuinfo\(^*\)
  - more stable
- pinned
Proposal for Consolidation

Ligand modification and Crosslinking


Big Picture

Conclusion

- Switch proteins can be turned on to control structural features of synapsis and store memories.
- New mechanism for memory storing, involves formation of stable molecules (complexes) with different electronic signatures.

But
Types of memory

- **Sensory memory**:
  - Very fast
  - Unstable
  - Low capacity

- **Short term memory**:
  - Fast
  - Unstable
  - Low capacity

- **Long term memory**:
  - Slow
  - Stable
  - High capacity

Kelvin E. E. *et al.* *Progress in Neurobiology*, 1982, 18, 181
Final word

• Different Types of memory demands different Mechanisms and applying unique pathway for all of them is unreasonable.

• And there is a long way to fully understand how it really works.
Acknowledgement

• Dr. Babak Borhan
• Dr. Xuefei Huang
• Labmates
• Family and Friends
The End

"Typical PhD brain"
Magnified 100x than original size!

- Jealousy region against high salaried engineer friends
- Beauty appreciation region
  - That professor is so handsome/beautiful
- Counting region
  - Number of missed festivals, birthdays and marriages
- Cooking Skills
  - (?) Free Food sensory organ
- Post-doc position database
- Publish the papers
- THESIS!
- Marriage/Babies avoiding region
- Social life...
- Fighting competitors
  - Area damaged due to excess caffeine to stay awake latenights!
  - Conference sleep inducing gland

Vishal Kaleel
http://phdhumor.blogspot.com