Brain – New Stuff
Memory & Consciousness

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Alzheimer’s Dementia


• Memory

• Consciousness
Memory in Time Domain

- **Seconds to minutes** – Frontal Lobe
- **Minutes to a few years** – Medial Temporal Lobe
- **Few Years to decades** – Association cortex
On September 1, 1953, a bilateral medial temporal lobe resection was carried out in which the amygdala, uncus, hippocampal gyrus, and anterior two-thirds of the hippocampus were removed. At the time, it was unclear that bilateral surgery of this kind would cause a profound memory defect.

Severe amnesia was evident, however, upon H.M.’s recovery from the operation, and his life was changed.
Brenda Milner

MONTREAL NEUROLOGICAL INSTITUTE AND HOSPITAL
McGill University

Another Memory Task
Memory

Man with a 15 seconds memory
### Comparison of Clinically Relevant Memory Systems

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<tr>
<th>Memory System</th>
<th>Examples</th>
<th>Awareness</th>
<th>Length of Storage</th>
<th>Major Anatomic Structures</th>
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<td><strong>Episodic memory</strong></td>
<td>Remembering a short story, what you had for dinner last night, and what you did on your last birthday</td>
<td>Explicit Declarative</td>
<td>Minutes to years</td>
<td>Medial temporal lobe, anterior thalamic nucleus, mamillary body, fornix, prefrontal cortex</td>
</tr>
<tr>
<td><strong>Semantic memory</strong></td>
<td>Knowing who was the first US president, the color of a lion, and how a fork and comb are different</td>
<td>Explicit Declarative</td>
<td>Minutes to years</td>
<td>Inferior lateral temporal lobes</td>
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### Memory Systems Comparison - continued

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<td><strong>Procedural memory</strong></td>
<td>Driving a standard transmission car and learning the sequence of numbers of a touch-tone phone without trying</td>
<td>Implicit Non-declarative</td>
<td>Minutes to years</td>
<td>Basal ganglia, cerebellum, supplementary motor area</td>
</tr>
</tbody>
</table>
| **Working memory** | Phonologic: keeping a phone number “in your head” before dialing Spatial: Mentally following a route, or rotating an object in your mind | Explicit Declarative | Seconds to minutes; information actively rehearsed or manipulated | Phonologic: prefrontal cortex, Broca area, Wernike area  
                          Spatial: prefrontal cortex, visual association areas. |
Episodic Memory

Semantic Memory
**Memory – Kandel et al, 2003. Synaptogenesis**

- Stimulate the siphon – withdrawal
- Like withdrawing the hand from a hot object
- 24 sensory neurons – 6 motor neurons
- Sensitization – a form of learned fear - tail
- Enhanced reflex response
- Single tail shock – enhanced reflex for minutes
- 5 or more stimuli – enhanced reflex for days
Memory – Gene Activation

Memory - Kandel

Histone Deacetylation
Manipulating Memories!

Memory - Adrenalin
Memory - Adrenalin

- Existing studies demonstrate that an increase of noradrenergic activity during a life-threatening event contributes to strengthening or "overconsolidation" of the memory for trauma

- Adrenergic modulation of local interneurons may contribute to the formation of fear memory by gating LTP in the conditioned stimulus pathways.

- Use of Propranolol for PTSD.


‘Memory eraser’ - LTP

- They could erase an animal’s hippocampal memory by blocking LTP.
- An unusual kinase called PKMzeta is necessary and sufficient for LTP maintenance.
- Trained rats in a shock-avoidance task and then injected some of the animals with a PKMzeta inhibitor.
- Inhibitor-injected animals explored the entire environment, appearing to have no memory of previous avoidance training.

Unstable Vs Stable Memory

- Karim Nader – McGill University
- Data show that consolidated fear memories, when reactivated, return to a labile state that requires de novo protein synthesis for reconsolidation.
- The lateral and basal nuclei of the amygdala (LBA) are believed to be a site of memory storage in fear learning.
- Consolidated fear memories, when reactivated during retrieval, return to a labile state in which infusion of anisomycin shortly after memory reactivation produces amnesia on later tests, regardless of whether reactivation was performed 1 or 14 days after conditioning.


NADER’s Method

- Nader's method is deceptively simple. He asks his patients to recall their bad memories and then gives them a so-called beta-blocker, a type of medication originally developed to treat heart conditions.
Propranolol Combined With Reactivation Therapy May Reduce PTSD Symptoms

- Adults with PTSD who actively recalled their traumatic event under the influence of propranolol once a week, for up to six weeks, reported a substantial decrease in PTSD symptoms compared with participants who took placebo. This decrease was evident from both the perspective of the patient and clinician.

- Propranolol blockade of reconsolidation may become a new therapy for some patients with PTSD.

Erased the emotional fear response in healthy people with arachnophobia.

- Merel Kindt, a professor of psychology at the University of Amsterdam.
- She compared three groups made up of 45 subjects in total.
- One group was exposed to a tarantula in a glass jar for two minutes, and then given a beta-blocker called propranolol.
- One was exposed to the tarantula and given a placebo.
- One was just given propranolol without being shown the spider, to rule out the possibility that propranolol by itself could decrease spider fear.

An Abrupt Transformation of Phobic Behavior After a Post-Retrieval Amnesic Agent
Smith, Kindt et al.
Biological Psychiatry, Volume 78, Issue 12, 880 – 886, Dec. 2015

- Dr. Kindt assessed the subjects’ anxiety when they were shown the spider the first time, then again three months later, and finally after a year.
- Those who got the propranolol alone and those who got the placebo had no improvement in their anxiety.
- But the arachnophobes who were exposed to the spider and given the drug were able to touch the tarantula within days and, by three months, many felt comfortable holding the spider with their bare hands. Their fear did not return even at the end of one year.
Optogenetics

How optogenetics works

- A light-sensitive protein from algae
- This protein is an ion channel that opens in response to blue light
- Take the gene for this protein
- ... and insert the DNA into specific neurons in the brain
- Neurons communicate by “firing.” This is an electrical signal created by opening & closing ion channels.
- So now you can cause neurons to fire just by flashing blue light!
- With the right combination of neurons, you can activate an entire brain circuit, to control specific behaviors (like movement)

Tracing and Tagging Memories: Science Fiction Becomes Science Fact

- Optogenetics. Christine A. Denny, PhD. Columbia.
- Dr. Denny uses genetically modified mice to record memories — turning those memories on and off at her command.
  - remarkable tagging of the neurons of a specific memory.
  - neurons had been tagged with the mouse’s experiences — as it was having them — of soft, earthy bedding, dark surroundings, and a plastic rock cave to hide under.
Image of neurons in the brain of a laboratory mouse taken while the mouse made a memory of a pleasant event.
• She places a small mouse gently into a lidless, transparent plastic box with a hard, white plastic floor, surrounded by bright lighting. The mouse huddles in a corner.
• Shen turns a key on a small box nearby. With a key turn, she sends a laser light through two narrow fiber-optic tubes attached to the mouse's skull, aimed at a few hundred cells in its brain.
• The mouse's perception in the plastic box is now rife with this specific stimulated memory. The mouse moves from the corner, sniffing and exploring. He grooms himself, a clear sign of feeling safe.
• When Dr. Denny turns off the laser input, the mouse retreats to the corner.

Lasers reactivate ‘lost’ memories in mice with Alzheimer’s
Forgotten memories have been reawakened in mice with Alzheimer’s disease, suggesting that the condition may not actually destroy our memories, but instead impair our ability to recall them.

To examine how memory is affected by Alzheimer’s disease, the researchers developed a way of visualising individual memories in mouse brains.

They genetically engineered mice with neurons that glow yellow when activated during memory storage, and red when activated during memory recall.

Two sets of these mice were created – one set that was healthy, and one with a condition resembling human Alzheimer’s disease.
Both sets of mice took a memory test.
First, they were exposed to a lemon scent and given an electric shock.
Then, a week later, they were exposed to the same lemon scent.
The healthy mice immediately froze in anticipation of being shocked again.
But the mice with Alzheimer’s disease froze almost half as much as the healthy mice, suggesting they did not remember the link between the smell and shock so strongly.

In healthy mice, the red and yellow neurons overlapped, showing that the mice were retrieving the lemon-shock memory from the same place it had been stored.
But in the Alzheimer’s mice, different cells glowed red during recall, suggesting that they were calling up the wrong memories.
This might help explain why people with Alzheimer’s disease commonly experience false memories, says Denny.
For example, many people with the condition incorrectly remember where they were during the 9/11 attacks. The mouse experiments suggest this may be because they are retrieving information from the wrong brain cells.
Using a genetic engineering technique called optogenetics, Denny’s team went on to reactivate the lemon shock memory in the Alzheimer’s mice. By shining a blue laser down a fibre optic cable into the brain, they were able to stimulate the yellow memory-storing neurons, prompting the mice to freeze when they smelled the lemon scent. This shows that “lost” memories may still exist in the brain, and can be recovered. Targeted drugs or techniques like deep-brain stimulation may help people with Alzheimer’s access their forgotten memories.

Memory manipulations, such as the retrieval of lost memories and the creation of false memories, were “once the realm of science fiction. But this experiment and other recent work have now accomplished these feats, at least in rodents.
MEMORY SEEKER - Nerve cells that hold a memory (green) in a mouse’s hippocampus can be coaxed into action with lasers, bringing the memory back up.

a, During contextual fear conditioning, a mouse is placed in a box where it undergoes an aversive experience, such as a footshock (yellow arrow), which causes it to freeze. Healthy mice recall this experience and freeze when placed back in the same box (not shown), but mice that model Alzheimer’s disease do not, indicating that they have long-term memory defects.

b, Roy et al. genetically tagged neurons that were activated during the aversive experience with a light-sensitive ion-channel protein (tagged neurons indicated in blue). They then removed the mice from the fear-conditioning environment and used pulses of blue light to repeatedly reactivate these neurons. In doing so, the authors rescued long-term memory in the model mice.
The formation of memories is the formation of our sense of self.

“Recording Memories & Playback”
Inserting memories into the brains of rats

- In a series of experiments, scientists at Wake Forest led by Sam A. Deadwyler trained rats to remember which of two identical levers to press to receive water; the animals first saw one of the two levers appear and then (after being distracted) had to remember to press the other lever to be rewarded.
- Repeated training on this task teaches rats the general rule, but in each trial the animal has to remember which lever appeared first, to inform the later choice.
The rats were implanted with a tiny array of electrodes, which threaded from the top of the head down into two neighboring pieces of the hippocampus, a structure that is crucial for forming these new memories, in rats as in humans.

The two slivers of tissue, called CA1 and CA3, communicate with each other as the brain learns and stores new information. The device transmits these exchanges to a computer.

To test the effect of the implant, the researchers used a drug to shut down the activity of CA1. Without CA1 online, the rats could not remember which lever to push to get water. They remembered the rule — push the opposite lever of the one that first appeared — but not which they had seen first.

The researchers, having recorded the appropriate signal from CA1, simply replayed it, like a melody on a player piano — and the animals remembered. The implant acted as if it were CA1, at least for this one task.

The Journal of Neural Engineering - 2013
Inserting memories into the brains of rats

- Turn the switch on, the animal has the memory; turn it off and they don't: that's exactly how it worked.
- In rats that did not receive the drug, new memories faded by about 40 percent after a long distraction period. But if the researchers amplified the corresponding CA1 signals using the implant, the memories eroded only about 10 percent in that time.

The Journal of Neural Engineering

Developing a hippocampal neural prosthetic to facilitate human memory encoding and recall

- First successful implementation in humans of a proof-of-concept system for restoring and improving memory function via facilitation of memory encoding using the patient's own hippocampal spatiotemporal neural codes for memory.

1 Wake Forest Baptist Medical Center, Winston-Salem, NC, United States of America
2 University of Southern California, Los Angeles, CA, United States of America
• We have constructed a model of processes by which the hippocampus encodes memory items via spatiotemporal firing of neural ensembles that underlie the successful encoding of short-term memory. Video Game with memory function.

• A nonlinear multi-input, multi-output (MIMO) model of hippocampal CA3 and CA1 neural firing is computed that predicts activation patterns of CA1 neurons during the encoding (sample) phase of a delayed match-to-sample (DMS) human short-term memory task.
• MIMO model-derived electrical stimulation delivered to the same CA1 locations during the sample phase of DMS trials facilitated short-term/working memory by 37% during the task.

• Longer term memory retention was also tested in the same human subjects with a delayed recognition (DR) task that utilized images from the DMS task, along with images that were not from the task. Across the subjects, the stimulated trials exhibited significant improvement (35%)

• These results demonstrate the facilitation of memory encoding which is an important feature for the construction of an implantable neural prosthetic to improve human memory.
“Memory gets better when artificial electrical stimulants help boost the natural brain waves.”

L. Marshall et al. *Nature* 2006; ‘showed that inducing slow oscillation-like potential fields by transcranial application of oscillating potentials (0.75 Hz) during early nocturnal non-rapid-eye-movement sleep, enhances the retention of hippocampus-dependent declarative memories in healthy humans.’

Electrodes were placed on the scalps of the sleeping subjects, and fluctuating electrical potentials were applied to induce cortical slow oscillations.

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**States of Consciousness**

- Awake
- Sleep
- Dream
Figure 1. Characterization of different patient groups (coma, vegetative state (VS), minimally conscious state (MCS), and US), and healthy individuals, along three traits: contents of consciousness (awareness), level of consciousness (wakefulness), and ability to produce voluntary behavior (mobility).

<table>
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<th>DoC</th>
<th>Definition</th>
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<td>Coma</td>
<td>A state of being completely unconscious. The person is not awake, and the eyes remain constantly closed. Also, there is no behavior suggesting the person is aware of self or surroundings.</td>
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<tr>
<td>Vegetative State, or VS Unresponsive Wakefulness Syndrome, or UWS Post-coma Unawareness, or PC-U</td>
<td>A state of being awake, with eyes open, and of not showing signs of behavior suggesting the person is aware of self or surroundings.</td>
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<tr>
<td>Persistent Vegetative State, or PVS</td>
<td>A VS or UWS that lasts for more than a month.</td>
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<tr>
<td>Minimally Conscious State, or MCS</td>
<td>A state in which the person has definite signs of behavior showing awareness of self or surroundings. Often, these behaviors may not be obvious or may not happen regularly.</td>
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</tbody>
</table>
| Emergence from MCS, or EMCS                                       | A state where the person can communicate in a way that can be understood. Or the person can recognize and use familiar objects.  
  ▪ To show communication, the person can answer yes or no to questions. The answers may be said aloud, written down, or shown with movements. Examples of these movements are head nodding or shaking, or thumbs pointing up or down. The answers must be correct and consistent when repeated.  
  ▪ For object use, the person can show that he or she knows how to use at least two different everyday objects, such as a cup or a comb. |
| Recovery of Consciousness                                         | A change in behavior that clearly shows the person is recovering awareness of self or surroundings. Recovery of consciousness happens when the health status of someone in a coma or VS/UWS improves to MCS. |
Minimally Conscious State - DBS

- 38-yr-old male who remained in an MCS following a severe traumatic brain injury ~ 6 years.
- He failed to recover consistent command-following or communication ability and remained non-verbal.
- Patient might express a minimal level of consciousness because of a primary impairment of the arousal system itself.
- By stimulating the intralaminar nuclei, the authors hoped to switch on the undamaged areas of cortex.
- Implanted DBS electrodes bilaterally within the central thalamus.

Minimally Conscious State - DBS

- The previously non-verbal patient became capable of naming objects and using objects with his hands — for example, bringing a cup to his mouth. Moreover, he could swallow food and take meals by mouth, meaning he was no longer dependent on a gastrostomy tube.
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When we fall asleep, consciousness fades yet the brain remains active. Why is this so?
Conscious or Unconscious

- Adrian Owen, a neuroscientist at the University of Western Ontario, asked Scott Routley to imagine playing a game of tennis, any acknowledgement would have been surprising.

- After all, Routley had been completely unresponsive for the 12 years since his severe traumatic brain injury. He was thought to be in a vegetative state: complete unawareness of self or environment.

- But, as Owen watched Routley’s brain inside a functional magnetic resonance imaging (fMRI) scanner, he saw a region of the motor cortex called the supplementary motor area—thought to play a role in movement—light up with activity. When he told Routely to relax, the activity ceased.

- And when he asked Routley to imagine walking around his house, he saw clear activity in the parahippocampal gyrus—a region of the brain that plays an important role in the encoding and recognition of spatial environment.
Functional MRI scans show activations associated with the motor imagery as compared with spatial imagery tasks (yellow and red) and the spatial imagery as compared with motor imagery tasks (blue and green). These scans were obtained from a group of healthy control subjects and five patients with traumatic brain injury.

Conscious or Unconscious

- After dozens of repetitions of these mental imagery tasks, Owen was sure that Routley was conscious.
- Then Owen went a step further: He asked Routley to answer yes-or-no questions by directing his imagination.
- Imagining playing tennis stood for “yes,” and walking around his house for “no.”
- Routely was able to correctly identify himself (“Is your name Scott”—“yes”; “Is your name Mike”—“no”), his location (“Are you in a hospital?”—“yes”; “Are you in a supermarket?”—“no”), the current year (“Is it 1999?—“no”; “Is it 2012?”—“yes”)
Routely was able to correctly identify himself ("Is your name Scott"—"yes"; "Is your name Mike"—"no"), his location ("Are you in a hospital?"—"yes"; "Are you in a supermarket?"—"no"), the current year ("Is it 1999?—"no"; "Is it 2012?"—"yes")

Routley, it turned out, was not in a vegetative state. In fact, he and patients like him required a new classification, which later researchers would call cognitive motor dissociation (CMD).

The results of this study show the potential for functional MRI to bridge the dissociation that can occur between behavior that is readily observable during a standardized clinical assessment and the actual level of residual cognitive function after serious brain injury.

Thus, among 23 patients who received a diagnosis of being in a vegetative state on admission, 4 were shown to be able to willfully modulate their brain activity through mental imagery; this fact is inconsistent with the behavioral diagnosis.

Another patient, Jeff Tremblay, was incorrectly diagnosed as being in a vegetative state for over a decade before researchers realized, again using fMRI, that he was conscious. Instead of asking him to imagine performing certain tasks, neuroscientist Lorina Naci showed him a short Alfred Hitchcock film.

Owen and Naci had previously detected a characteristic pattern of brain activity in healthy participants that was closely synchronized to the plot of the Hitchcock film. When Naci and her team showed Tremblay the film inside an fMRI scanner, they saw this same pattern of complex mental response.

Brain-wide synchronization of neural activity across subjects. (A) Movie viewing elicited significant \((P < 0.05; \text{FWE cor})\) cross-subject correlation across the brain. (B) No cross-subject correlation was observed in the resting state. (C) The scrambled movie elicited significant \((P < 0.05; \text{FWE cor})\) cross-subject correlation only within primary and association visual and auditory cortex; none was observed in higher-order, supramodal cortex. (D) The intact movie elicited significantly \((P < 0.05; \text{FWE cor})\) more cross-subject correlation than the scrambled movie bilaterally in parietal, temporal, motor, and dorsal/ventral frontal/prefrontal cortex.

Patient 1 only auditory area activation – vegetative state
Patient 2 – CBD – auditory, visual & executive processing

Vegetative State

- Is the patient really a ‘vegetable’
- Depends upon extent of damage
- Can they hear and follow instructions?
- Of course not !!!!!!!!

Owens et al, Science; 2006.
Recovery from a Coma

- Terry Wallis recovery from a coma after 19 years.
- Minimally Conscious State
- Neurons slowly reconnecting over all these years
- ?? potential

‘Conscious’ vs ‘Unconscious’ Vision!

- Story of 2 interesting patients.
- DB – ‘Blindsight’
- CY – ‘Visual Agnosia’
Blindsight

Visual Agnosia

- John
- Can see but cannot recognize !!!!
- Can draw objects, copy them but cannot identify
- “out of focus in my mind but not in my eye”
Daughter or Mother