Neurobiology of Learning & Memory
‘To get back my youth I would do anything in the world, except take exercise, get up early, or be respectable’

Oscar Wilde, The Picture of Dorian Gray, 1891
Exercise and the brain: something to chew on

Henriette van Praag

Neuroplasticity and Behavior Unit, Laboratory of Neurosciences, Intramural Research Program, National Institute on Aging, National Institutes of Health, Baltimore, MD 21224, USA
Physical activity

- The most effective way to maintain a healthy body and mind

Prevention of:

- Hypertension, heart disease, type II diabetes, osteoporosis and depression

PE not respected in US

- Study after study shows that risk of cardiovascular, metabolic, and metastatic diseases is mitigated by exercise and diet
Exercise and healthy diet

- Good for the brain
- Improves cognition

Delay

- Age related memory decline

Protects

- Against brain damage caused by stroke
- Promotes recovery
Fit kids

- High IQ
- Better learning

Take a run

- Learn faster
- No ceiling effect!!
- Being active makes a functional difference
<table>
<thead>
<tr>
<th>Nutrition</th>
<th>• Has an impact on cognitive function</th>
</tr>
</thead>
<tbody>
<tr>
<td>High fat foods</td>
<td>• Increase risk of cognitive decline</td>
</tr>
<tr>
<td>Supplements</td>
<td>• Omega fatty acids</td>
</tr>
<tr>
<td></td>
<td>• Spices, teas, fruits</td>
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<td>Mostly work with exercise</td>
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</table>
In intervention studies healthy sedentary adults between the ages of 60 and 85 years participate in an exercise regime several times per week over the course of several months to several years. Cognition and fitness is assessed before and after the intervention. Although studies vary in duration, intensity and type of exercise, overall physical activity improves cognitive function.
Recall Gall

- Localizationist view
- The mind is the brain

Recall Wernicke and Broca

- Proposed a theory of language
- Complex behavior is a product of interconnected areas of the brain

The brain is more like an active ecosystem.

- Not like a preprogrammed computer.
- No single center for .... language, vision, emotion, social behavior, consciousness .... or memory.
What is memory?

- Is it the act of searching for the memory?
- Is it forming it in the first place?

Is a memory still there if even if ...

- Memory in its quiescent state is not detectable.
- One cannot separate the act of retrieving and the memory itself.

Here, there, and everywhere...

- Bits and pieces of a single memory are stored in different networks of neurons.
- We bring the pieces together when it is time to recall that memory.
Karl Lashley: Law of Mass Action
The severity of memory impairment is correlated with the size of cortical area removed, not with the specific location.
Loss of Recent Memory After Bilateral Hippocampal Lesions

William Beecher Scoville
Brenda Milner

Memory as a Life's Work
An Interview with Brenda Milner

The Journal of Neurology, Neurosurgery and Psychiatry (1957; 20:11–21)
Diagrammatic cross-sections of human brain illustrating extent of attempted bilateral medial temporal lobe resection in the radical operation. (For diagrammatic purposes the resection has been shown on one side only.)
H.M.

“Every day is alone in itself, whatever enjoyment I’ve had, and whatever sorrow I’ve had .... Right now, I’m wondering. Have I done or said anything amiss? You see, at this moment everything looks clear to me, but what happened just before? That’s what worries me. It’s like waking from a dream; I just don’t remember.”

Memory is a distinct mental function.

Loss of medial temporal lobe structures destroys the ability to convert new STM to LTM.

It is only in the hippocampus that sensory information necessary for forming LTM come together.

Short-term memory and long-term memory are stored separately.

Disproved Lashley’s theory of mass action.

HM had good LTM for events prior to the surgery – therefore hippocampus is not the site for LTM storage.
Mirror drawing task
Gollin figures – incomplete pictures task
Explicit memory or declarative memory: objects, places, facts, people, and events.

1. Short term explicit memory
2. Converted to long term memories
3. Stored in parts of the cortex that correspond to the senses involved – the same areas that originally processed the information.
Hippocampus is critical for episodic memory.

**Episodic**

- The ability to place facts and events in time and refer to them.
- It involves looking at the past an event and to the future to envision summer vacation.
- Associated with a specific moment and place.

**Semantic**

- Detached from personal experience.
- Cognitive rather than autobiographical.
- Enables one to retain facts and everyday functions, including categories of events, objects, spatial knowledge and symbolic description.
Implicit memory or procedural memory: skills, habits, and conditioning.

Implicit memories of skills, habits, and conditioning are stored in the cerebellum, striatum, and amygdala.
Surgery helps Squirrel Hill violinist overcome epilepsy.

by Adrienne M. Lederich
TRIBUNE REVIEW
TUESDAY, NOVEMBER 19, 2019

After Atlanta Curtis woke from surgery that removed much of the right side of her brain to stop epileptic seizures, doctors heard her violin and told her they wanted to teach her “musical memory.”

Nearing a hospital gown, and with the right side of her head shaved to reveal a red, curving incision, Curtis began playing a violin solo composed by Johann Sebastian Bach in the 17th century.

“They kept saying they were worried about muscle memory and to play the Bach because it’s the hardest stuff in the world to remember,” said Curtis, 51, of Squirrel Hill.

“What I didn’t realize is that’s not what they meant. They were afraid I wouldn’t pick up the violin and not know what to do. They’re memory is the memory that there’s music in the world. They were wondering if I knew what to do with a violin.”

Curtis, a recent afternoon this week, National Epilepsy Awareness Month, performed the violin in her living room, telling her story. She’s lived with epileptic seizures since she was a child and has learned to live with them in her daily life.

“My mother was the one who had seizures and started to have them, which is an understandable response, but I think there’s a lot of questions that still need to be answered," said Curtis. "My doctors told me, ‘Your child has a medical problem, but you could make it a very serious problem, but out of the way."

So her mother, Anna Curtis, gave her daughter some breastfed. She introduced her to the piano and dance lessons. When the waltz, Curtis picked up the violin.

“Since that did was put me in an orchestra. And that’s what saved me,” Curtis said. “You have 100 people on stage who are going to make music and feels really great.”

Harmonious therapy

The early exposure to music likely built Curtis’s developing brain, shifting impulsive, impulsive and spatial navigation to the underlying, left side.

“I don’t know if she would have survived all without music,” said Charles Carmack, a professor who became Curtis’s music teacher at the University of Rochester’s Eastman School of Music. "She was an 11-year-old that was more visible of music at those functions in the past 10 years that have given her the music." Curtis ultimately lost her purse brain surgery.

She graduated summa cum laude from the Cleveland State University School of Medicine, and with support from an independent research foundation, began her study of music.

As the legend went, they called several musical groups in the city that was interested in the orchestra. When the seizures started, Curtis felt a growing sense of nervousness and stress. Sometimes, she had to sit on the floor, thinking she was going to pass out and have a seizure.

Surgical success

In April 2000, Curtis had four grand mal seizures — severe seizures that cause the body to convulse. She realized she was losing control of her life, so she traveled to Cleveland Clinic for a consultation.

"Once I came in, my husband was right there with me, smiling," she said. "I had a lot of friends who were there. But the surgery was a success. They removed the part of my brain that was causing the seizures."

"By June, two months later, I was sitting in Cleveland Clinic with Hans Luderer." A series of tests showed doctors that Curtis’s seizures were originating in her right temporal lobe, buried deep in her brain’s outer layer. If doctors could remove that part of her brain, the seizures would end. Her first and second surgeries didn’t work. Doctors didn’t want to do a third surgery for fear they’d remove too much brain and paralyze her left side or bilateral.

Because of the seizures, she didn’t think anyone would ever hire her as a full-time violinist. Instead, she worked part time for three orchestras in northeastern Ohio and played concerts throughout the state.

She met her future husband, Walter Jackson, in 1983 when she was playing in a string quartet in Wheeling, W.Va. She knew she would marry him after her first date with the quartet.

"It was love at first sight," Curtis said. "We had never met at all before the date. We met and I immediately knew it. It was love at first sight." Jackson said, "Growing anything else would have detracted from my ability to convey that message."

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learning

influence

perceptual information

memory
Three Types of Implicit Learning

- Habituation
- Sensitization
- Classical Conditioning
Most simple form of learning

Initial response to stimuli:
very defensive -

Repeated exposure to stimuli:
Response is muted - Eventually ignored.

Purpose:
Animal needs to learn which stimuli to safely ignore

Eliminates inappropriate or exaggerated defense responses

Important for:
Organizing perception
Sensitization – mirror image of habituation

After a noxious stimulus

the sensitized animal respond more strongly to all stimuli.

Purpose:
Instead of ignoring a stimulus – it is a form of learned fear. Survival.

It teaches the animal to attend and respond more vigorously to almost any stimulus

Konrad Lorenz: “An earthworm that has just avoided being eaten by a blackbird ... is indeed well advised to respond with a considerably lowered threshold to similar stimuli because it is almost certain that the bird will still be nearby for the next few seconds.”
Aversive Classical Conditioning

A neutral stimulus must always precede the aversive stimulus – that way the animal will come to predict it.

Pavlov: shock a dog’s paw. The shock caused the animal to raise and withdraw its leg – a fear response.

Pavlov found that after several trials in which he paired the shock with a bell – first sounding the bell then the shock – the dog would withdraw his paw whenever the bell sounded.

Classical conditioning an association is formed between a pair of stimuli that occur in rapid sequence.

Teaches the animal to associate an unpleasant stimulus with a stimulus that ordinarily elicits no response.
bell

response

shock
Cellular basis of learning and memory

- Learning changes neural responsiveness
- Enhanced functioning of existing neural circuits or the establishment of new ones.
Kandel, Eric
In Search of Memory: The Emergence of a New Science of Mind
Aplysia californica

Aplysia has external organs: gill and the siphon
Why aplysia?

- Small nervous system
- Gigantic cells
- Identifiable neurons

Simple reflex

- Gill withdrawal reflex
- Gill and siphon withdraw upon strong stimulation of the tail.

Defensive reflex – this reflex could be modified by the three forms of learning.
Sensitization in *aplysia*: a form of learned fear

In order for this type of sensitization to occur, an animal must *remember* a previous aversive stimulus, and they find that how long that memory lasts is a function of the number of repetitions of the stimulus.
Two important principles:

The strength of the synaptic communication between nerve cells can be changed for many minutes by applying different patterns of stimulation.

The same synapse can be strengthened or weakened by different patterns of stimulation.
**Stimulus** (tone or shock)

**Response** (degree of alertness)

**Stimulus** (S1-benign; S2 noxious)

**Response** (firing of cell)

**Habituation**

**Sensitization**

**Classical conditioning**

**Synaptic strength is not fixed** – it can be altered in different ways by different patterns of activity.
<table>
<thead>
<tr>
<th>What do we really know?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Memories for events change with time?</td>
</tr>
<tr>
<td>Memories for traumatic events change with time?</td>
</tr>
<tr>
<td>Vivid memories can be created for events that did not actually happen of which people can be very confident.</td>
</tr>
<tr>
<td>Just thinking about doing something may create a memory of having actually done it.</td>
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</table>
A picture is worth a thousand lies: Using false photographs to create false childhood memories

KIMBERLEY A. WADE and MARYANNE GARRY
Victoria University of Wellington, Wellington, New Zealand
and
J. DON READ and D. STEPHEN LINDSAY
University of Victoria, Victoria, British Columbia, Canada
How to create a false memory

• Participants: 20 “confederates” recruited a family memory to be in the study

• 3 true photos and one false photo

• The “Step-Wise” interview procedure
  – 3 interviews over ~2 week period
Figure 2. Mean percent of events remembered by event type and interview.
Example Interview

Interview 1

Interviewer: And again, if you want to tell me as much as you can recall about this event without leaving anything out.

Subject: Mm ... no, never actually thought I'd been in a hot air balloon, so there we go.
Interviewer: You can’t remember anything about this event?
Subject: Nah. Though it is me ... no memory whatsoever.
Interviewer: If you want to take the next few minutes and concentrate on getting a memory back, something about the event.
Subject: No, yeah I honestly ... no I can’t. That’s really annoying.

Interview 3

Interviewer: Same again, tell me everything you can recall about Event 3 without leaving anything out.
Subject: Um, just trying to work out how old my sister was; trying to get the exact ... when it happened. But I’m still pretty certain it occurred when I was in form one (6th grade) at um the local school there ... Um basically for $10 or something you could go up in a hot air balloon and go up about 20 odd meters ... it would have been a Saturday and I think we went with, yeah, parents and, no it wasn’t, not my grandmother ... not certain who any of the other people are there. Um, and I’m pretty certain that mum is down on the ground taking a photo.
Debriefing

The subjects’ comments during debriefing suggests that they were not suspicious of the photographs. For example, when told that one of the photos was a fake, Subject A.G. replied, “That’s amazing, ’cause I honestly started to talk myself into believing it! ... I still feel in my head that I actually was there; I can sort of see images of it, but not distinctly, but yeah. Gosh, that’s amazing!”
Misinformation effect

• When people who witness and event are later exposed to new and misleading information about it, their recollections become distorted.
Two experiments are reported in which subjects viewed films of automobile accidents and then answered questions about events occurring in the films. The question, “About how fast were the cars going when they smashed into each other?” elicited higher estimates of speed than questions which used the verbs collided, bumped, contacted, or hit in place of smashed. On a retest one week later, those subjects who received the verb smashed were more likely to say “yes” to the question, “Did you see any broken glass?”, even though broken glass was not present in the film. These results are consistent with the view that the questions asked subsequent to an event can cause a reconstruction in one’s memory of that event.
Basic Paradigm

• subjects see a series of slides or a film depicting a car accident, robbery, or some other naturalistic eyewitness event
• asked a series of questions
• manipulate the way one question is asked to determine effects on recall
Nearly 200 subjects viewed 30 slides depicting an automobile accident.

- Half saw a red Datsun approaching a STOP sign; the other half saw it approach a YIELD sign.

- Immediately after viewing the slides half of the participants were asked: "Did another car pass the red Datsun while it was stopped at the stop sign?".

For the others 'stop' was replaced by 'yield'.

20 minutes of filler activity followed, then a recognition test was performed on the photos to the left.
## Results

<table>
<thead>
<tr>
<th>Condition</th>
<th>% Correct</th>
</tr>
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<tbody>
<tr>
<td>Consistent</td>
<td>75%</td>
</tr>
<tr>
<td>Inconsistent</td>
<td>41%</td>
</tr>
</tbody>
</table>

After the viewing, half the participants received a suggestion that the traffic sign was a yield sign. When asked later what traffic sign they remembered seeing at the intersection, those who had been given the suggestion tended to claim that they had seen a yield sign.

Those who had not received the phony information were much more accurate in their recollection of the traffic sign.
• Subjects see a video depicting a car accident
• Asked, “How fast were the cars going when they________ each other?”
• Varied the intensity of the verb that described the collision:
  smashed, collided, bumped, hit, and contacted
A week later in the absence of the film clips the participants were presented with additional questions about the car accident including the key question asking whether there was any broken glass.

There was actually no broken glass in the film.

Participants in the smashed condition gave a mean speed estimate of 10.46 mph as compared to 8.00 mph in the 'hit' condition.

32% of the participants who had been previously asked about the speed of the cars when the verb 'smashed' was used recalled seeing broken glass as compared to 14% of those asked using the verb 'hit'
Conclusion:

The study demonstrates that eyewitness testimony can be easily influenced by the wording of a question. The findings also suggest that over an amount of time memory for an event may be considerably distorted by post event information.
Alzheimer’s Disease

- Alzheimer’s Disease (AD)—A type of dementia characterized by progressive neurological degeneration and a profound deterioration of mental functioning.
  - Early onset—before age 65
    - Risk factors include familial clustering of cases, increasing age, and Down syndrome.
### Table 14.3
Characteristics of the Three Stages of Alzheimer’s Disease

<table>
<thead>
<tr>
<th>Stage</th>
<th>Other Terms</th>
<th>Intelligence</th>
<th>Personality</th>
<th>Language</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Early</td>
<td>Forgetful</td>
<td>Apathetic</td>
<td>Comprehension nearly normal</td>
</tr>
<tr>
<td></td>
<td>Mild</td>
<td>Disoriented</td>
<td>Anxious</td>
<td>Vague words in talk</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Careless</td>
<td>Irritable</td>
<td>Naming may be impaired</td>
</tr>
<tr>
<td>II</td>
<td>Middle</td>
<td>Recent events forgotten</td>
<td>Restless</td>
<td>Comprehension reduced</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Math skills reduced</td>
<td></td>
<td>Paraphasias jargon</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Naming becomes wordy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Poor self-monitoring</td>
</tr>
<tr>
<td>III</td>
<td>Late</td>
<td>Recent events fade fast</td>
<td>Unresponsive</td>
<td>Unresponsive</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Remote memory impaired</td>
<td>Withdrawn</td>
<td>Mute</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Family not recognized</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Source: Adapted from Davis, G. A. (1993). A survey of adult aphasia and related language disorders (2nd ed.). Boston: Allyn & Bacon. All rights reserved. Adapted with permission.
The Cellular Basis of Alzheimer’s Disease

• See Scientific American Spotlight “Senile Words” which has suggestions about the factors that lead to AD.

• Cellular basis of AD
  – Neurofibrillary tangles
  – Senile plaques
  – Amyloid beta protein
AD: Cellular Pathology

[Image showing amyloid plaque and neurofibrillary tangle]

http://nihseniorhealth.gov/alzheimersdisease/symptoms/images/tangles_crop.jpg
AD: Brain Pathology

**Brain: Normal Elderly**

**Brain: Alzheimer’s Disease**

Preclinical AD
Mild AD
Moderate and Severe AD

- Extreme Shrinkage of Cerebral Cortex
- Severe Enlarged Ventricle
- Extreme Shrinkage of Hippocampus
Alzheimer’s Disease: The Degeneration of Neural Pathways

• **Nucleus basalis of Meynert**—cholinergic neurons that originate in this structure of the basal forebrain and synapse in the neocortex and hippocampus degenerate.

• Administration of cholinergic antagonists in animals leads to memory deficits.
Alzheimer’s Disease: The Degeneration of Neural Pathways

• Treating with ACh agonists has not resulted in great improvements suggesting that other neurotransmitters may be involved.

• Glutamate may not be cleared from the synaptic cleft and adds to the degeneration of neurons in the affected areas. There is also evidence that amyloid beta protein may be a causative agent in the disorder.
Alzheimer’s Disease: Genetics

- There is a link between chromosome 21 and AD.
- Another gene identified is *ApoE* on chromosome 19.
- Some people have one or two *ApoE4* alleles and have a greater risk of having late-onset AD.
- The product of *ApoE4* is not an effective antioxidant for amyloid beta protein as are the products of other alleles.
- This may indicate a need to develop more effective methods to increase antioxidants in the brains of AD patients.