Learning and Memory

Lulu Durand, 2012

… those short, plump little cakes called 'petites madeleines,' which look as though they had been moulded in the fluted scallop of a pilgrim's shell. … I raised to my lips a spoonful of the tea in which I had soaked a morsel of the cake. No sooner had the warm liquid, and the crumbs with it, touched my palate than a shudder ran through my whole body, and I stopped, intent upon the extraordinary changes that were taking place. An exquisite pleasure had invaded my senses but individual, detached, with no suggestion of its origin (Marcel Proust, *In Search of Lost Time*, 1913)

René Depasse

This is the famous quotation about memory by Marcel Proust.
It describes how the past can be re-experienced.
How simple sensory triggers can bring forth complex memories.
How these memories are at first indistinct and mysterious and only later become clear.
How emotions are the glue that ties memories together.

Where to get madeleines in Toronto?
Try Madeleines bespoke pastry
http://www.madeleines.ca/

For green-tea madeleines – Uncle Tetsu's at Bay and Dundas.

Brain and Mind: Course Outline

1. Introduction. Brain anatomy. Stroke. Neurons. Excitation. Action potentials. Synaptic transmission.. Body sensations. Braille.

2. Moving to the Music. Muscles. Stretch reflexes. Basal ganglia. Cerebellum. Parkinson's Disease. Balance. Hearing. Speech and music.

3. Sensation and Perception. Taste and smell. Hunger and satiety. Vision. Visual fields. Motion. Recognizing faces and objects. Illusions.

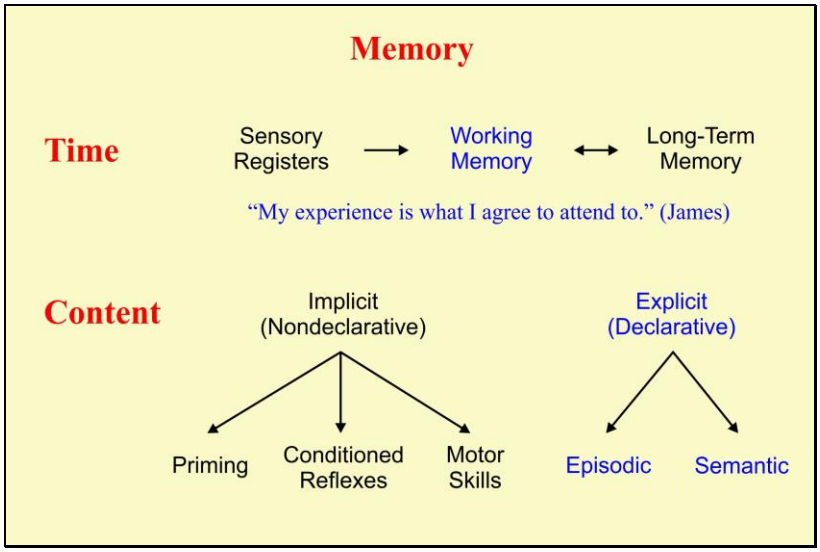
4. Consciousness. Sleep, meditation, coma, epilepsy. Locked-in syndrome. Attention. Consciousness. Theory of mind. Split-brain studies – interpreter.

5. Learning and Memory. Synaptic changes. Motor skills. Priming. Episodic vs semantic memory. Amnesia. Alzheimer's Disease.

6. Language and Emotion. Language. Humans vs chimps. Aphasia. Dyslexia. Basic emotions. Autonomic Nervous System. Love and Hate. Music.

7. Thought and Will. Executive functions. Psychopathy. Brain networks (attention and default). Determinism. Free will.

8. Madness and Wisdom. Psychiatric diagnosis. Anxiety. Schizophrenia. Depression. Addiction. Maturation of brain. Mental speed. Ageing. Wisdom.

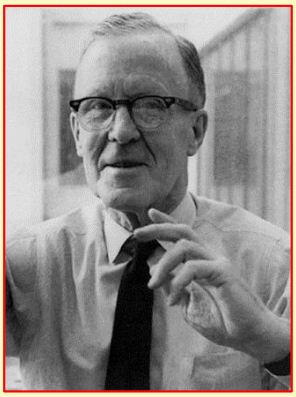


We can consider memory from two different viewpoints – time and content.
In terms of time, information initially comes into our mind/brain through the sensory registers. Consciousness occurs in working memory. Long term memory receives new memories from working memory and allows working memory access to past experience in order to interpret what is happening in the present.

In terms of content, memories are either accessible to consciousness (explicit) or not (implicit). The only way we can demonstrate that a memory is explicit is to describe it – thus the term "declarative."

Neuronal Cell Assemblies

In his 1949 book *The Organization of Behavior,* Donald Hebb proposed that perception and memory are based on groups of neurons that activate each other through reverberatory circuits. When neurons are synchronously activated, some metabolic or structural change occurs in their synapses to facilitate and preserve the connections between them ("neurons that fire together wire together"). They could thus serve as memory engrams – activation of one neuron will automatically activate the other neurons in the cell assembly.

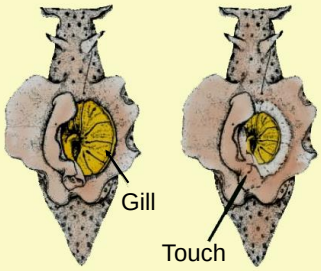


Donald Hebb (1904-1985)

Donald Hebb was Professor of Psychology at McGill University.

Aplysia (lateral view):

Gill Withdrawal Reflex:



Simple Learning System

When the nearby skin is touched, the gill withdraws. This reflex is controlled by neurons in the abdominal ganglion.

With repeated touching the reflex **habituates**. The reflex can be **sensitized** by shocking the tail. The withdrawal can also be **conditioned** to occur following a shock if the shock is repeatedly presented just before the touch.

Eric Kandel received the Nobel Prize in 2000 for studying the synaptic mechanisms of these changes.

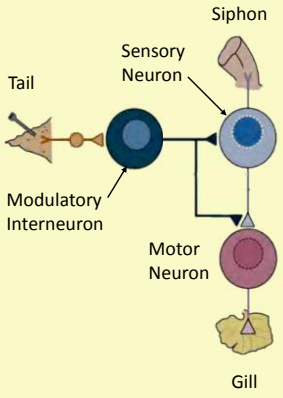
The Aplysia is a sea slug or sea hare. This rather ugly animal (the name means "unwashed") has contributed a great deal to our understanding of learning.

Habituation is a very simple form of learning. The animal learns that a stimulus has no meaning and therefore requires no response.

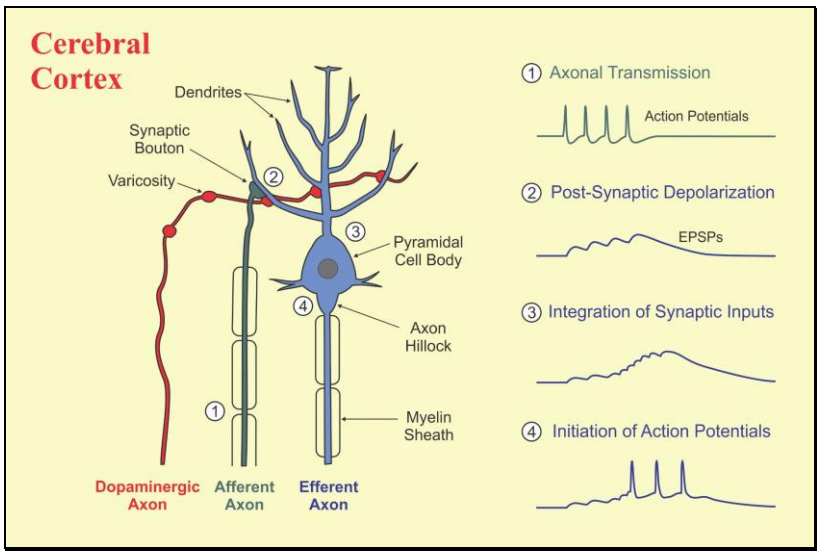
Habituation, sensitization and conditioning of the gill withdrawal reflex are meditated through interneurons which alter the effectiveness of the synapse between the sensory and motor neurons. In the Aplysia, these interneurons use serotonin as a transmitter.

The modulatory interneuron acts both pre- and post-synaptically. In the short-term it causes greater (or lesser) release of neurotransmitter at the synapse. In the medium term it can increase (or decrease) the production of transmitter and receptors. In the long term it can cause more synapses to be made (or unused synapses to be pruned).

Synaptic Plasticity

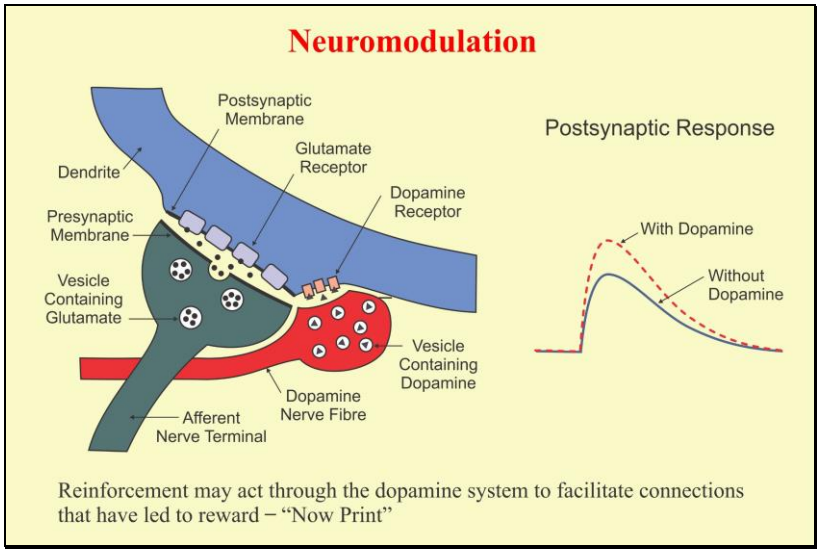


The same processes that occur in the Aplysia occur in the human brain. As well as serotonin, other modulatory transmitters involved in learning are dopamine and norepinephrine.



This slide illustrates some simple synaptic connections in the cerebral cortex. We have seen this slide before in the session on the synapse. Then we were concerned with how information comes into the cortex and actuates a response. This time we focus on the dopaminergic axon (red). Information comes to the cortex from the thalamus. This information is transferred to the pyramidal neuron, which then sends it on to other neurons.

The dopaminergic neuron acts on the synapse between the afferent axon and the dendrite of the pyramidal cell.



This slide looks more closely at that synapse.
The afferent activity comes in and releases the excitatory transmitter glutamate.
How effective the glutamate is depends on the activity at the adjacent dopamine synapse. If dopamine is released at the same time, the postsynaptic response is greater (dashed red line)

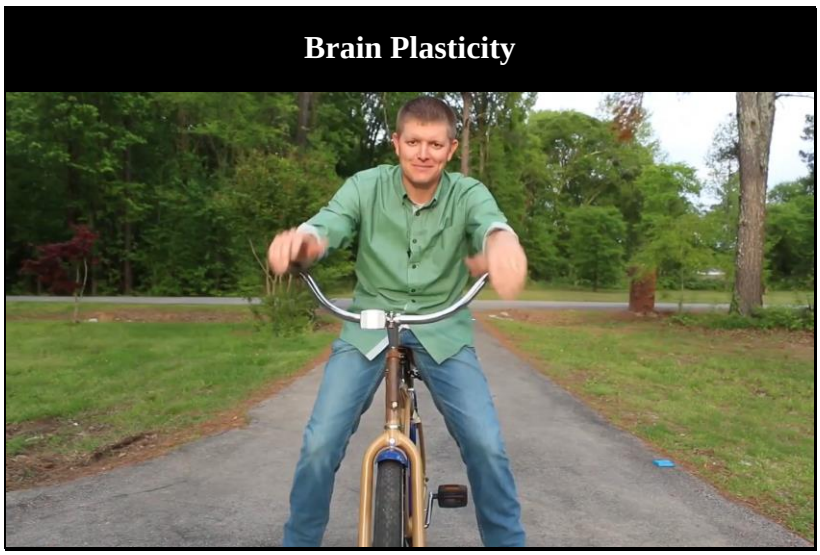
In this way the dopamine system might reinforce synaptic activity, making the synapse more efficient.

One old idea was that the dopamine system mediated a “Now Print!” process. The brain keeps trying to find the best way to respond. When it finally hits on the correct way to act, there is a feeling of great pleasure. This activates the dopamine system which reinforces the synapses that have been active during the successful behavior.

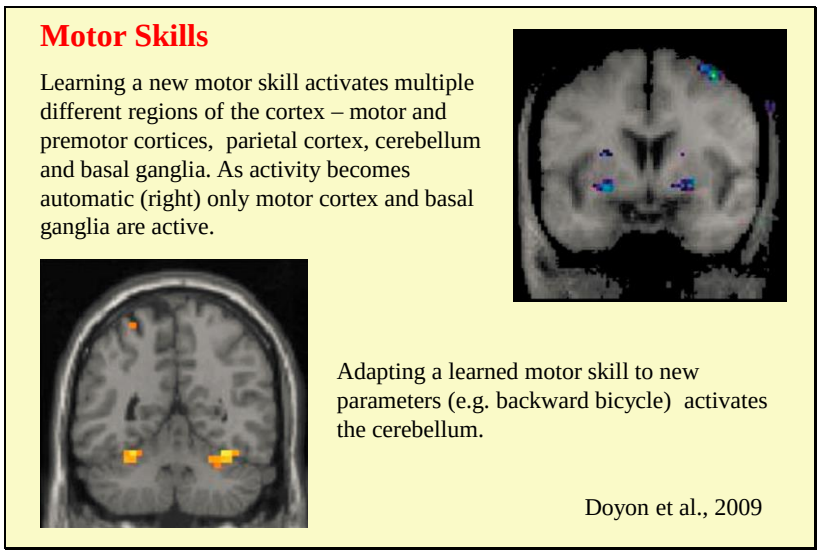
The Backward Brain Bicycle

Now we can consider some of the simply learned activities such as riding a bike. These quickly become automatic. We cannot really describe what we are doing. When we learn these activities, we do so more by trial-and-error than by consciously thinking what we should do.
Automatic behaviors or habits are very efficient – they do not require much mental energy. But they are very difficult to change.

The backward bicycle video is available at
https://www.youtube.com/watch?v=MFzDaBzBlL0



By dint of hard work, however, the brain can relearn how to do things. The neurons have to be re-wired – synapses have to change.
The ability to change our behavioral programs is called plasticity. As we grow older we become less and less plastic.
However, we need not be completely hidebound – we should try something new everyday.



The brain scan at the upper right shows what happens as we learn a new motor skill.
Initially widespread regions of the brain are active. As the skill becomes learned it uses a few neurons in the motor cortex and the basal ganglia. The motor cortex initiates the behavior and the basal ganglia operate the programs.
The cerebellum is an important center for changing the programs (lower left).

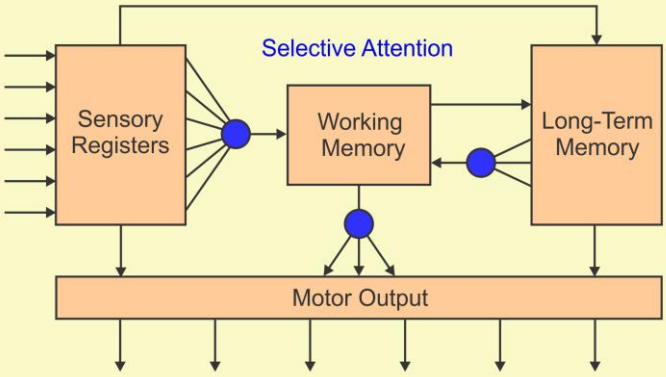
Constraint-Induced Movement Therapy

After a stroke the return of function to the paralyzed limb is very variable. Stretching is essential in the early weeks to months to prevent the limb from going into contractures.

When function begins to return, it is essential to use the limb as much as possible. However, the patient usually wants to use the normal limb and not the weak one. Edward Taub and his colleagues have recommended constraining the good limb so that the patient is forced to use the weak limb. This causes a significant improvement in function.

The basic idea of this approach to stroke rehabilitation is "Use it or lose it!"
This is good for many more things than motor function.
As we grow old we should occasionally force ourselves not to take the easy way but to do things that are difficult – take a new route to the library, read something about which we are unfamiliar, meet someone new.

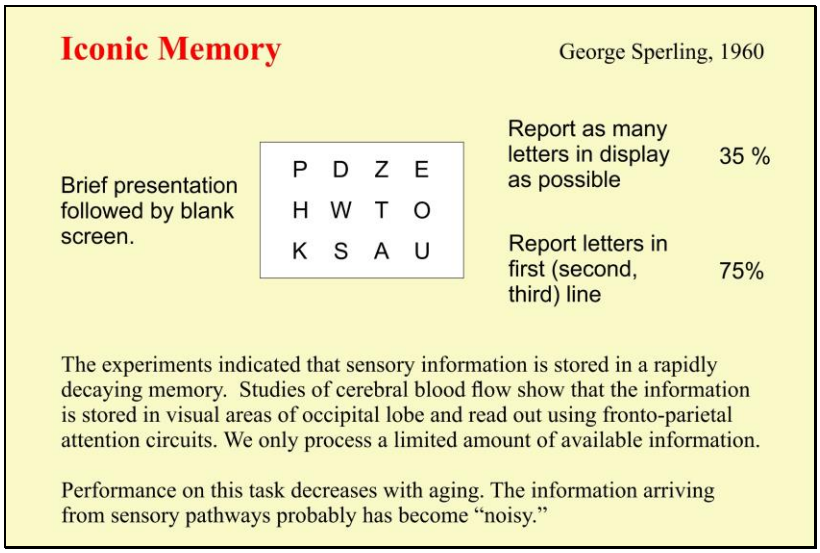
Architecture of Cognition



Having considered implicit memories – how we learn motor skills and automatic behavior – we can now look at how explicit memory works.
This diagram shows the flow of information in the human brain/mind. Everything is much more inter-related than is suggested by the separate boxes, but it sometimes helps our understanding to look at things separately.

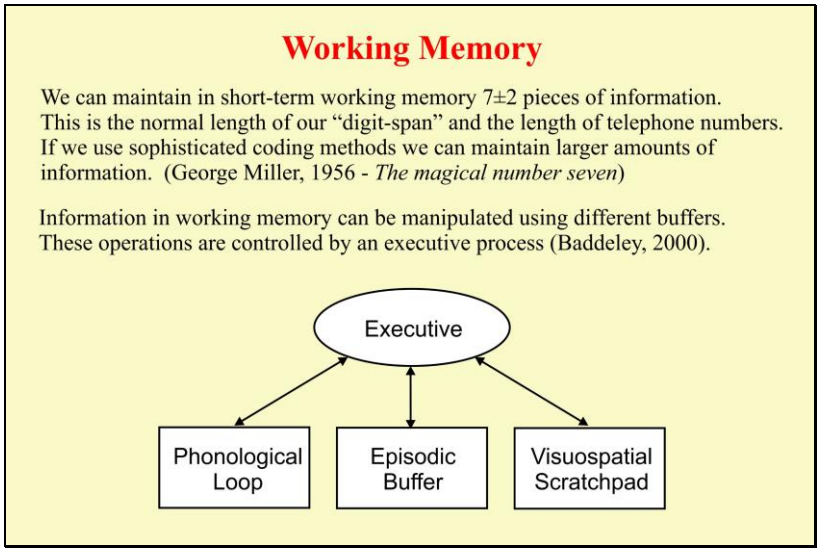
Information comes in via the senses and is stored in sensory registers.
Working memory is where consciousness operates.
Working memory can transfer information in and out of long term memory, and can initiate motor responses.

All of the transfers are under the control of selective attention (blue).
Attention determines what we perceive and what we ignore, what we put into memory and what we remember, what actions we decide to respond with.



A large array of letters is briefly stored in a visual register called iconic memory.
If we try to read out all of the letters, most of them disappear before we get to them.
However, if after the presentation we are told to read out just one particular line, we are much more accurate – all the letters are there but only for a brief time.

In the auditory system, there is an analogous sensory register called echoic memory. This is the memory that allows you to read the paper while your spouse is talking. When he or she says, "You haven't been listening," simply say, "Oh yes, you were saying … " and fill in whatever words pop up from echoic memory.



Information is read out of sensory registers into a working memory system.
This has limited capacity – about 7 separate pieces of information. The length of old-style telephone numbers.

This limited capacity makes us unable to attend to everything – we have to select only some inputs among all possible inputs.

Working memory uses a variety of buffers to store information while it is operating. Alan Baddeley has proposed several buffers. The phonological loop stores speech-sounds. This is where we remember a telephone number after hearing it. The visuospatial scratchpad allows us to manipulate two- and three-dimensional representations. The episodic buffer frames our experience into a set of events.

Another buffer might use somatosensory codes. This might be helpful in figuring out dance movements or athletic strategies.

Also, a musical buffer is likely separate from the phonological buffer.

N-Back Task

A sequence of letters is presented visually:

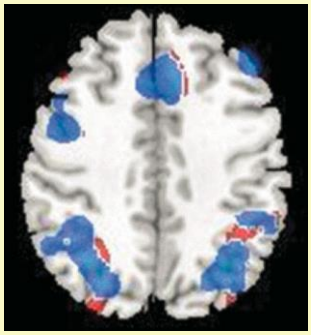
C D K P R J M D D P T C

The subject responds when a letter is the same as that one-letter before (D) – "1-back." More difficult versions of the task require responding to letters that are the same as letters '2-back" (R):

F D L P R J R Z D W S C

or "3-back" (M):

B F K F D M R J M P T C



Blood flow studies show activation of left inferior frontal region (phonological loop) and prefrontal cortices (executive) as well as parieto-occipital regions (visual)

One way to evaluate working memory is the N-Back Task. You have to keep the last few letters "in mind" (i.e. in working memory) so that you can check if one of them repeats. As the letter go on you have to update the letters in working memory.

Episodic Memory

Explicit long-term memory is generally divided into semantic memory for facts and episodic memory for events in one's own life. Endel Tulving was the first person to distinguish these two kinds of memory:

"Episodic memory is a recently evolved, late-developing, and early-deteriorating past-oriented memory system, more vulnerable than other memory systems to neuronal dysfunction, and probably unique to humans. It makes possible mental time travel through subjective time, from the present to the past, thus allowing one to re-experience, through autonoetic awareness, one's own previous experiences. Its operations require, but go beyond, the semantic memory system."

Endel Tulving (1927 -)

Now we move from short-term memory to long-term memory.
The most important conceptual advance in our understanding of long-term memory is the idea that there are two basic kinds of long-term memory: semantic memory for facts (What is the capital of France?) and episodic memory for one's personal experience (What did I have for breakfast this morning?).
When we recall facts they come back without any sense of personal involvement. We just "know" them.
When we recall episodes in our life they come back with a personal flavor – to some extent we re-experience them. We "remember" them.

Autonoetic = self understanding
Endel Tulving has also proposed that episodic memory can also be directed to the future – we can imagine what we might be doing tomorrow. Mental time travel can go forward as well as backward.

Study these words. You will be tested later for your memory of them.

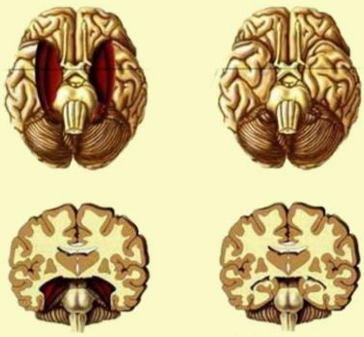
ASSASSIN
OCTOPUS
AVOCADO
MYSTERY
SHERIFF
ELEPHANT
CASHMERE
FLAMINGO
PENDULUM
OBELISK

A simple test of episodic memory is to remember a list of words.
After a period of time, you will be asked to recall as many words as possible.
You have thirty seconds to memorize the list. Your behavior will be improved if you visualize what they represent, associate them with each other, tell yourself stories about them, etc. We remember what we process deeply. The concept of "depth of processing" comes from Gus Craik.

HM

Henry Molaison
(1926-2008)

Patient HM suffered from severe epilepsy. In 1953, the medial halves of both his temporal lobes (including hippocampus and amygdala) were removed in an attempt to control his seizures.



Now we shall look as some of the disorders of memory – amnesia.
The most famous patient in neuropsychology is Henry Molaison – HM.
Dr. William Scoville, a neurosurgeon in Hartford Connecticut removed both his medial temporal lobes in order to control his epileptic seizures.

Brenda Milner (1918 -)

Pure Amnesia

After the operation, the Canadian neuropsychologist Brenda Milner found that HM was unable to form any new memories (anterograde amnesia) and had difficulty remembering past memories (retrograde amnesia) particularly for the three years preceding the operation.

However, unlike other patients with amnesia, his other mental abilities were unaffected. His general IQ was 112. His language was normal. His forward digit span was 6.

After the surgery he was unable to make new memories – anterograde amnesia – and he remembered only some of his past – partial retrograde amnesia.

Brenda Milner – almost 98 years old – is still active at the Montreal Neurological Institute.

Luke Dittrich, the grandson of William Scoville, has published a recent book *Patient HM: A Story of Memory, Madness and Family Secrets.*

KC became amnesic after a motorcycle accident. His brain was extensively damaged particularly in the medial temporal regions. Although his thought processes were clear, he was unable to learn new information or to remember ongoing experience.

He remembered semantic knowledge from before the accident and knew some "facts" about his life. However, he was unable to recollect any events from his personal past. Even when told about memorable things that happened to him, he denied any recollection or sense of familiarity.

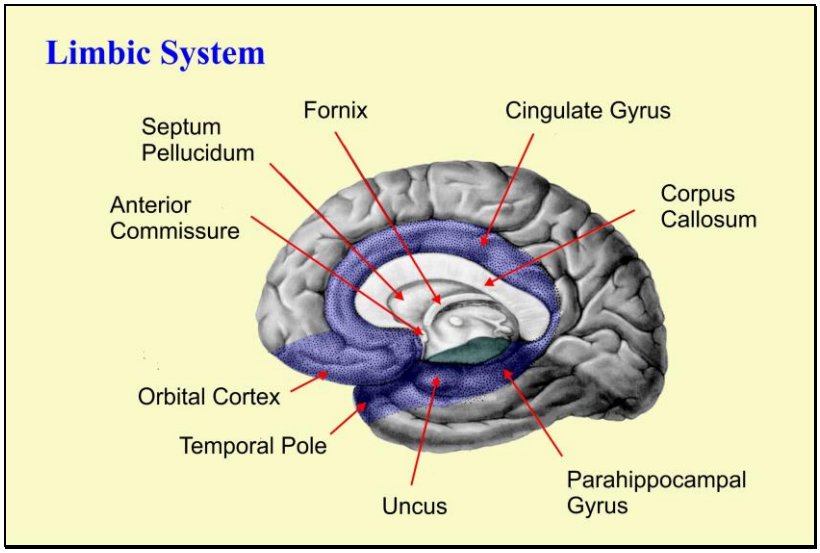
As well, he was unable to imagine his future.

The Man Without any Personal Past

Kent Cochrane (1951–2014)

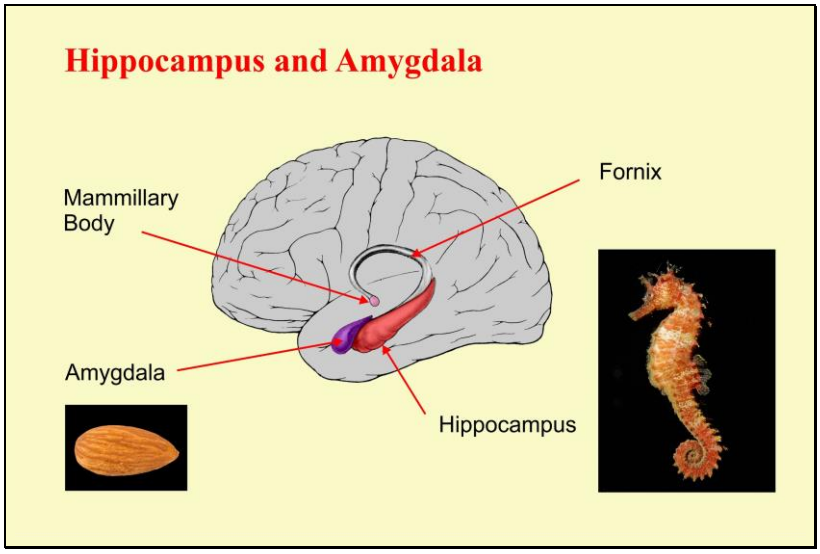
One aspect of amnesia following head injury is the lack of any episodic flavor to a patient's memory of the past.
It is possible that this might be due to concomitant frontal lobe lesions.

This amnesic patient studied by Endel Tulving and his colleagues, could not lay down new memories but could recall information from his past.
However, what he could remember from the past was mainly semantic – the facts of his life. He had little personal involvement in the events of his past life, even those that were very emotional.



Two slides from the first presentation.

HM's surgery removed the hippocampus and parahippocampal gyrus in the limbic system. These areas are essential to the laying down of new memories and the recall of old memories.



The hippocampus projects to the mammillary body in the thalamus via the fornix. The mammillary body then connects to the thalamus and cortex.
The anterior hippocampus is adjacent to the amygdala which is associated with emotion. This may account for the close relationship between memory and emotion. We remember most clearly

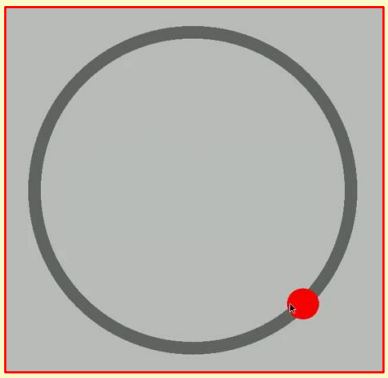
those things in our lives that evoked great emotions – the birth of a child, the death of JFK, the events of 9/11.

Now, we should check to see how well your hippocampus worked – What words do you remember from the list that I gave you 5 slides ago. Patient HM would remember none.

Most people will remember three or four. Often the first couple of words, sometimes the last. The older you are the fewer you remember.
However, if you were really creative (if you used great depth of processing) then you might even remember them all.

Motor Skills

HM was able to learn a simple motor skill such as that needed in the Rotary Pursuit Test. During a week of exposure to the task his performance got progressively better over the first four days even though on each day he could not remember doing the test before. The improvement was maintained when he was tested again a week later.



Normal subjects performed better on the task than HM and continued to improve over more than four days.

Although HM could not remember what happened to him after the operation, he could learn a simple motor skill – such as keeping the cursor on a rotating disc.
This type of implicit learning is mediated by the basal ganglia and cerebellum and does not involve the hippocampus.

Complete these word fragments. Do the easier fragments first.

Priming occurs independently of whether the words were recognized as being on the study list and persists much longer than recognition memory.

Priming occurred normally in patient HM. It is mediated by the visual cortex in the occipital lobe.

A__A__IN	ASSASSIN
O_T__US	OCTOPUS
_E_TUC_	LETTUCE
_YS__RY	MYSTERY
_UFF_A_	RUFFIAN
_L_P_A_T	ELEPHANT
_U_R_ET	QUARTET
MO_O___M	MONOGRAM
_G_O_T_C	AGNOSTIC
OB__I_K	OBELISK

HM was also able to demonstrate "priming," an implicit memory process.

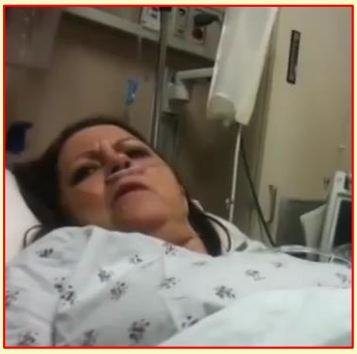
In this test you are asked to complete some word fragments.
Do as many as you can – do not get stuck on one, go on to the next. Write down which ones you can complete.
You will find that some of these are easier than the others – the red ones.
They are the ones that were in the list that you tried to memorize about fifteen minutes ago. It does not depend on whether you actually were able to memorize them – it just requires that you experienced them.

Transient Global Amnesia

The patient suffers from a complete inability to store new memories and has some difficulty recalling memories from the past few weeks. The patient is understandably confused but there are no other neurological symptoms.

The patient is typically between 55 and 75 years old. The attack lasts between 2 and 8 hours.

The patient often keeps asking the same question over and over again.



The etiology is unknown (perhaps some migraine or epileptic equivalent). Other disorders should be ruled out with a brain scan and EEG. Prognosis is good. The patient will not remember much about the attack.

Temporal lobe surgery is important for understanding how amnesia works, but it is an uncommon cause of amnesia.
We shall now turn to some more common amnestic syndromes.

The first is transient global amnesia. This presents with confusion and an inability to store new memories.
The characteristic repetition of the same question over and over again is like a broken recording. Other causes of confusion must be ruled out. Once the physician has made sure of the diagnosis, there is no treatment.
https://www.youtube.com/watch?v=N3fA5uzWDU8

Characteristic hemorrhages in the mammillary bodies

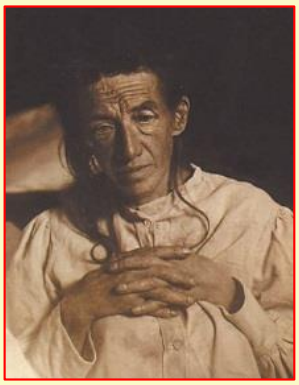
Korsakoff's Psychosis

Alcoholism may cause acute thiamine (vitamin B1) deficiency. This can lead to hemorrhages in many different regions of the brain. The most commonly affected areas are the mammillary bodies. Damage to these causes acute amnesia. In the resultant Korsakoff's psychosis, amnesia is usually accompanied by **confabulation**. The patient fills in the memory gaps by inventing stories, some based on snippets of old memories and others wildly fanciful. Confabulation may be related to additional damage elsewhere in the brain, particularly in the frontal cortices.

The mammillary bodies are the main outflow connection of the hippocampi.

This clip shows the Psychiatrist G. K. Shaw interviewing a patient with Korsakoff's Psychosis. In the olden days there were 12 in a shilling and "3 and 9 pence" meant 3 shillings and 9 pence. This patient's memory is lost but arithmetic is preserved.
The complete video (which also describes other effects of alcohol on the brain) is available at
https://www.youtube.com/watch?v=wDcyBXJAZNM

Ich habe mich sozusagen verloren



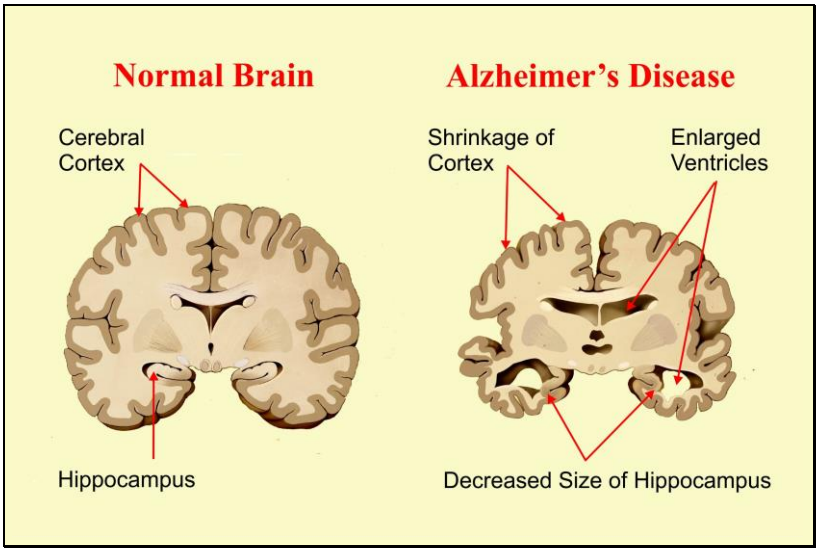
Auguste Deter (1850-1906)

What is your name?
Auguste.
Family name?
Auguste.
What is your husband's name?
.....I believe ... Auguste.
Your husband?
Oh, so!
How old are you?
Fifty-one.
Where do you live?
Oh, you have been to our place
Are you married?
Oh, I am so confused.
Where are you right now?
Here and everywhere, here and now, you must not think badly of me.
Where are you at the moment?
We will live there.

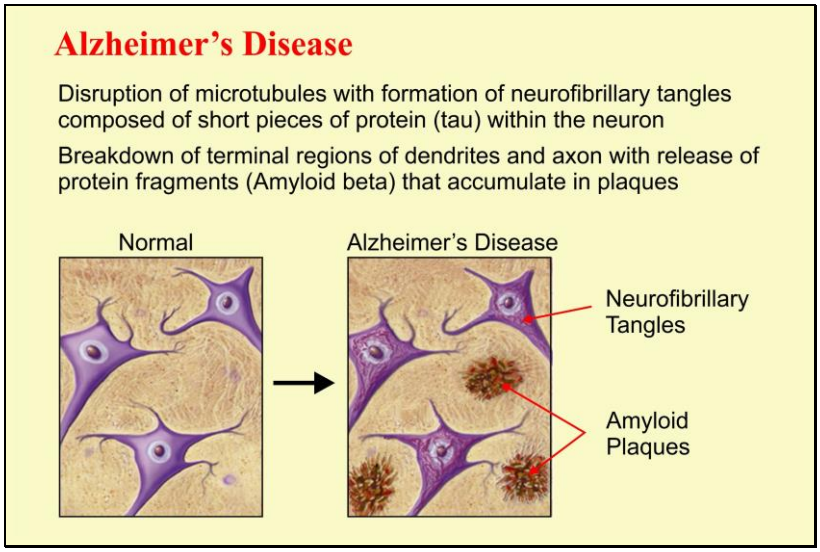
The most common type of amnesia is that associated with Alzheimer's Disease: "dementia"

Auguste Deter was the first patient described by Alois Alzheimer in 1901. Amazingly the original notes from her clinical examination were preserved in the hospital records. As was her photograph.

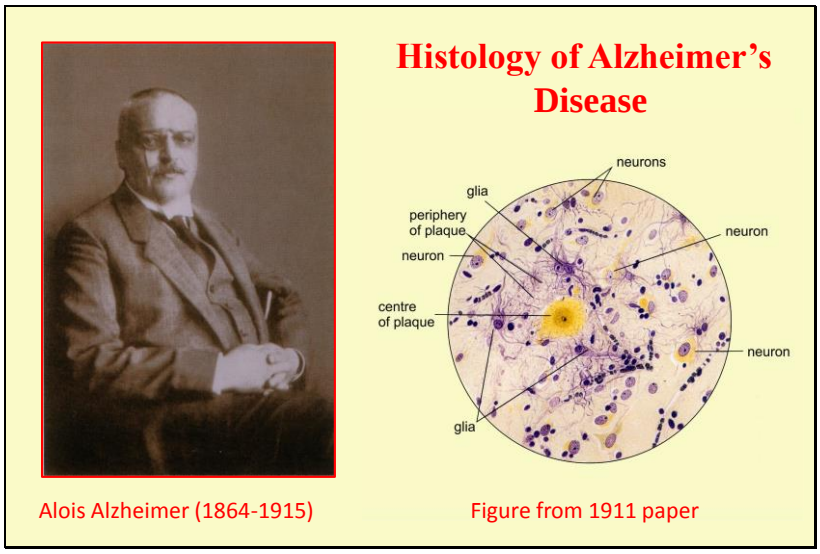
The German translates as "I have, you might say, mislaid myself." Syntactically correct. Semantically devastating.



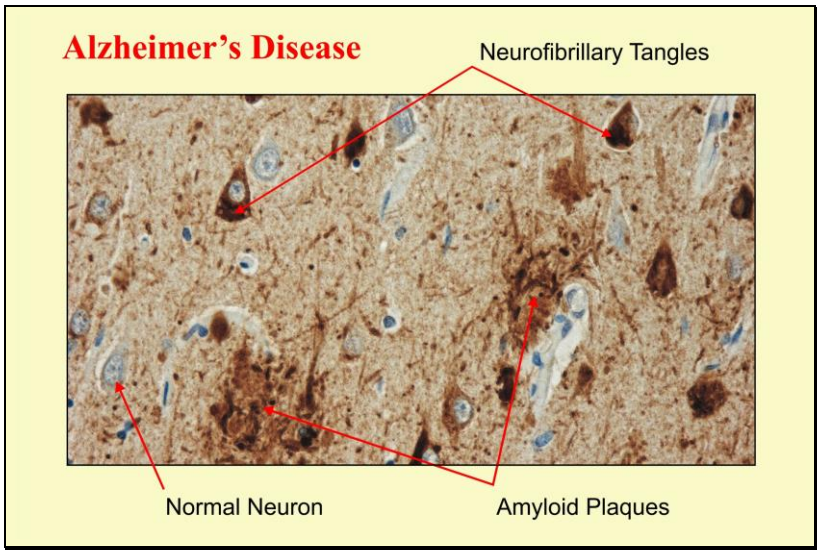
Alzheimer's Disease is associated with widespread degeneration of the brain. These are slices of the brain cut in the coronal plane.
The hippocampi are particularly affected. The hippocampus is an area of the brain that is essential for laying down and recalling memories. The main presenting symptom of dementia is a loss of memory.



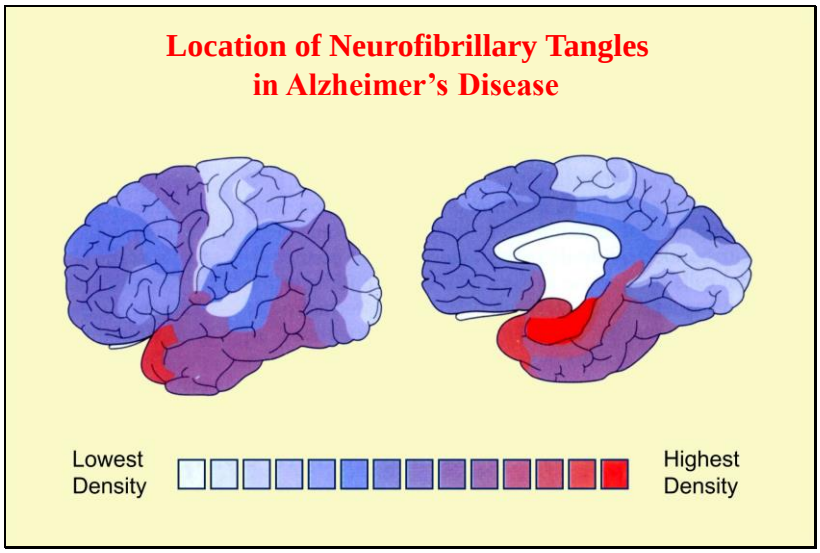
We do not know for certain the cause of Alzheimer's Disease. Some current hypotheses suggest that it may be a disorder of axonal transport. The microtubules that carry things along the nerve fibers break down and the broken pieces form neurofibrillary tangles within the neurons. Perhaps because the distal regions of the axon are no longer properly supplied, the terminals break down and release material into the extracellular space that forms amyloid plaques. Both of these abnormal processes disrupt the normal communication between neurons. A recent study has suggested that we may be able to clear the amyloid deposits from the brain using antibodies that have been developed to attack human amyloid fragments.



This slide shows one of Alzheimer's original illustrations of the histology of presenile dementia. The amyloid plaque is surrounded by reactive glial cells. The particular stain in this section does not show the neurofibrillary tangles.



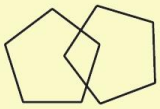
This is a recent microscopic section showing dark brown tangles within some of the neurons, as well as the plaques. The normal neurons are bluish whereas the diseased neurons are full of brown-stained tangles. The very elongated bluish regions are capillaries.



Neurofibrillary tangles are most prominent in the medial and anterior temporal areas.
This fits with the patient's most prominent symptom being amnesia.
Note that the sensory and motor areas of the brain are much less affected.

Mini Mental Status Exam

(i) Orientation to time (5 points)
(ii) Orientation to place (5 points)
(iii) Registration (3 points)
(iv) Attention – subtract 7 from 100 (5 points)
(v) Recall (3 points)
(vi) Language – naming (2 points), repetition (1 point), following commands (3 points), reading (1 point), writing (1 point)
(vii) Spatial – draw the following figure (1 point)



Normal: 24-30; Mild Impairment: 18-23; Severe Impairment 0-17

One of the major fears that comes with growing old is the fear of becoming demented.
So to dispel that fear we shall go through the Mini Mental Status Exam

Time – year season month date day
Place – country province city building floor
Registration – apple penny table
Attention – 100 93 86 79 72 65
Recall three words after an interval – apple, penny, table
Language: name watch, pencil; repeat "no ifs ands or buts"; raise your hand, close your eyes, wave; Reading and Writing (a simple sentence) .
Spatial

Frontotemporal Dementia

Anomic aphasia is only one part of the syndrome of fronto-temporal dementia (FTD).

Patients with FTD present with behavior problems. If they are working, they make foolish decisions. Socially, they become quite "disinhibited." The patient may have bursts of impulsive or aggressive behavior. Often there is a general apathy.

One variant of this syndrome – Pick's disease shows abnormal tau-protein accumulations.

Another cause of dementia and memory loss is frontotemporal dementia. The patients often have an anomic aphasia although this video does not show it. The common findings are memory loss,

behavioral problems and apathy. This particular patient shows severe apathy. He does not remember his daughter's name, and has difficulty remembering his wife's.
https://www.youtube.com/watch?v=E09agP3swYs

There is an intense sadness to "Bye-bye blackbird."

Study these words. You will be tested later for your memory of them.

CANDY
SOUR
SUGAR
BITTER
GOOD
TASTE
TOOTH
CHOCOLATE
CAKE
EAT

Another memory test. You have a minute to study these words.

Which of these words were on the studied list?

TASTE	CANDY
SWEET	SOUR
POINT	SUGAR
CAKE	BITTER
HOUSE	GOOD
	TASTE
	TOOTH
	CHOCOLATE
	CAKE
	EAT

Sometimes, we remember things that did not occur or that did not occur when we think they did. Our memory system is creative in how it puts things together to make sense. Unfortunately this can lead to false beliefs, especially when real memories are put together with a therapist's suggestions.

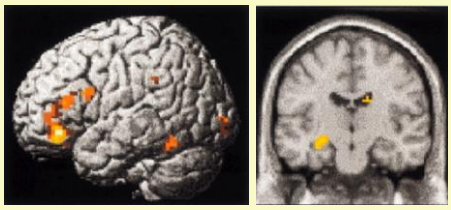
This is an immediate recognition test. Which of these words was on the list.
Many of you will claim that the word SWEET was on the list that you studied.

It was not. Many words on the list were related to sweetness but the word SWEET was not on the list. This illustration (from Dan Schacter) shows that memories can sometimes be false.

False beliefs have occurred in court cases wherein people were accused of sexual abuse or Satanic cults.
We must be very careful not to suggest things when witnesses are asked about their memories, and we must always seek corroborative evidence.

Encoding

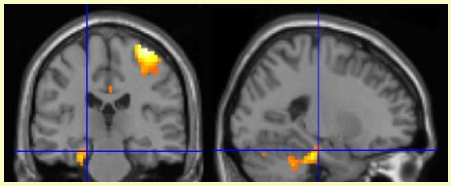
This involves interactions between frontal cortex (particularly left) and hippocampus. It is facilitated by "depth of processing"



Otten et al., 2001

Retrieval

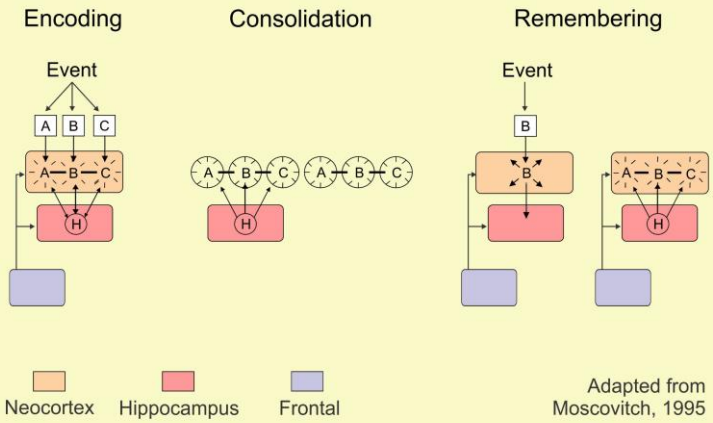
This can be triggered by a cue (recognition) or by deliberate memory search (recall). It involves interactions between the right frontal cortex and the medial temporal lobe.



Daselaar et al., 2001

The hippocampal regions are involved in both encoding and retrieval.
Regions of the frontal cortex control the laying down and raising up of memories.

Time-Course of Long-Term Memory



Long-term memories change over time. The hippocampus serves to combine the separate parts of an event into a combined memory. This is the process of consolidation. As a memory becomes "consolidated" it may no longer need the hippocampus to initiate its retrieval.

Then we can remember in two different ways. We can specifically search for a memory (frontal and hippocampal activation – far right) of a stimulus (like the taste of Proust's madeleines) may trigger the memory.
This might explain why patients with amnesia can remember events from long ago, i.e. those that were well consolidated, but not those from the recent past, i.e. those are not yet consolidated.

Preserving Memory

Eat well: decrease sugar and alcohol; increase fish and vegetables

Sleep well: probably aids consolidation of new (and old) memories, and helps us forget what is irrelevant

Keep physically active: exercise increases the flow of blood to the brain

Socialize: human beings are social animals; interaction with others keeps the mind active.

Check your eyes and ears: processing information is important – you can't remember what you did not hear

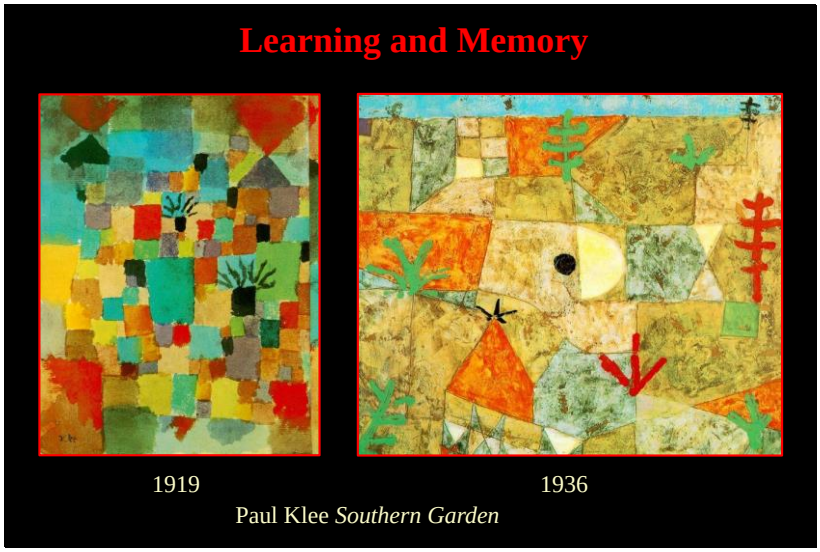
Use memory aids: make lists of things to do; use weekly pill boxes for remembering when to take medications; keep everything in its place.

Try new things: take courses; read about what you do not know; travel to new places; increase your "cognitive reserve;" use it or lose it.

One thing at a time: leave multi-tasking to younger people; keep focused (do not do something else until what you have finished what you are doing)

I have told you a lot about memory. Will this help you remember your spouse's birthday or where you put your car-keys? Probably not.
So this is a list of hints for preserving our memories as we grow old.

There is at present no convincing evidence that any vitamin supplement (vitamin E, for example), hormone or drug works to prevent dementia.



In April 1914, Paul Klee travelled to Tunisia with August Macke and Louis Moilliet. They were struck by the brilliant colors of North Africa. Klee wrote in his diary "The color possesses me. There is no need to try to grasp it. It possesses me. Here is the meaning of this happy moment: the color and I are one. I am a painter."
He had learned the significance of color, and the possibility that color could be independent of form.
He returned to these memories often during his career. In a watercolor just after the first world war, and in a small oil painting just before the second. Memories make us. Remembering comforts us.

You are what you remember. Seek out the new. Lay down memories. Treasure them.