

MEMORY AND COGNITION

Your knowledge in this Neuroscience course should be closely related to the Neurological Exam. In the “Mini Mental” part this exam you will ask the patient if you can test their memory. To do this, state the name of three unrelated items (dog, pencil, ball) and then ask the patient to repeat the three items. This is testing their “**short term or working memory**”. Then ask the patient to remember these three items, because you will ask him/her to repeat them 3-5 minutes later. Make certain all three objects have been registered and provide distracters during the delay period to prevent the patient from rehearsing the items repeatedly. Then, (after 3-5 minutes), ask your patient to recall the three unrelated items. This is testing what is called “**recent memory**”. Finally, you will test your patient for what is called “**remote memory**”. This is done by asking the patient about historical or verifiable personal events of the past.

The following overview should help you understand the biology underlying these different types of memory tests. **PLEASE** read this with interest and enthusiasm and realize that what you will be tested on relates to what you will use as a physician! The Practice Questions are 100% indicative of the level of understanding expected of you. Memory is a very interesting yet still poorly understood aspect of cognition.

AN OVERVIEW OF MEMORY

Sensory Memory

All incoming information is held briefly (1/2 to 2 seconds) in sensory memory as a copy of the actual sensory information (for example, visual stimuli will be held briefly in visual cortex/area 17) . Because it is sensory information, the information in sensory memory is primitive and unanalyzed. If a group of letters is very briefly flashed on a screen in front of you, you can remember 9-12 of them (visual or “iconic” memory). However, most of the information in sensory memory fades away before we can do anything with it. However, if we pay **attention** to the information it moves on for further processing.

Short term or working memory

Imagine that you are asked to remember a telephone number that is new to you. If you read the phone number in the yellow pages, the visual cortex receives the information (sensory memory). Since you are paying a lot of attention to the number, this information gets “recoded” from a visually based code into a phonologically based one. (That is, you translate the visual stimuli into their corresponding words, and you then rehearse and retain these words.) The duration of short term memory is **15 -30 seconds**. You could

probably keep the telephone number in your short term or working memory for more than 30 seconds, but only by saying it over and over again in your head. This is called "rote rehearsal" or "maintenance rehearsal". However, if anything happens to interrupt your rote rehearsal, the information will be lost. The prefrontal cortex (PFC) plays an important role in protecting the contents of short-term memory. This area lies in the frontal lobe, rostral to the premotor areas that we studied soooooo darn hard in "Motor Systems". We know that PFC is not responsible for the storage, per se, of information in short-term memory, because patients with PFC lesions have normal capacity (as assessed, e.g., by the digit span test). But these patients are highly susceptible to distraction and to the effects of interference, and thus often experience problems with short-term memory in their daily lives.

The capacity of short term memory is around 7. George Miller, a very famous cognitive psychologist, coined the phrase "the magical number seven, plus or minus two," to describe the capacity of short term or working memory. We can increase the absolute capacity of memory by combining bits of information into meaningful units, or chunks. The capacity of short term memory is approximately 7 "chunks."

The PFC is a convergence zone, since it receives connections from visual and auditory sensory systems (for example). These inputs enable the PFC to know what is going on in the outside world and to integrate the information it gathers. It receives information from other areas involved in long term memories (to be discussed next) and thus it can retrieve stored information (facts, personal experiences) relevant to the task at hand.

As I am typing (slowly!) this, information is flowing into and out of my short term or working memory. When you are talking or answering questions, the information must be brought into working memory for you to manipulate, and your words and answers come out of working memory. As you try to understand the words on this page, your ability to understand these concepts depends on your working memory (and to some extent your long-term memory).

The process of finding information in long term memory and bringing it back to working memory (so it can be used) is called retrieval. Sometimes, when we have learned information, but can't find it when we want to use it, the problem is not that the information is not in long term memory, it is that we cannot find it in long term memory; therefore we cannot retrieve it. Since long term memory appears to be organized mainly according to meaning, information will be easiest to retrieve if we focus on meaning and understanding as we are learning.

Long term memory

As mentioned earlier with short term memory, information about the external world comes into the brain through the sensory systems that relay the signals to the neocortex, where sensory representations of objects and events are created. In addition to

reaching the PFC, pathways from these sensory cortical areas converge on the medial temporal lobe and in particular on areas surrounding/adjacent to the hippocampus (parahippocampal and perirhinal cortical areas). The parahippocampal and perirhinal cortices serve as convergence zones where information from different modalities can be put together in a form of a global memory of a situation (if this did not happen, memories would be fragmented!). The parahippocampal cortex receives projections primarily from the parietal cortex/dorsal visual stream, the perirhinal cortex primarily from temporal lobe/ventral visual stream. These regions then send the information to the entorhinal cortex, then onto to the hippocampus. The interconnections in the hippocampus are extremely detailed, so you can ask us about them if interested (those in the back row can jar JKH, but Mark will have to just endure up in the front!). Eventually the integrated information leaves the hippocampus and is sent **BACK** to the cortical areas where the input originated. In this way, cortical areas involved in processing a stimulus can also participate in the long term storage of memories about that stimulus.

The memory is stored via synaptic changes that take place in the hippocampus. When some aspect of the stimulus situation recurs, the hippocampus participates in the reinstatement of the pattern of cortical activation that occurs during the original experience. Each reinstatement changes cortical synapses a little (this is learning!). Because the reinstatements depend on the hippocampus, damage to the hippocampus affects recent memories but not old ones that have already been consolidated in the cortex. Old memories are the result of accumulations of synaptic changes in the cortex as a result of multiple reinstatements of the memory. Eventually, the cortical representations come to be self-sufficient, and at that time the memory becomes independent of the hippocampus. (Some investigators feel that memory consolidation occurs during sleep). Thus, it appears that that explicit memories are stored in the cortical systems that were involved in the initial processing of the stimulus and that the hippocampus is needed to direct the storage process.

Many psychologists believe that once information is in long-term memory, it stays there forever. If we are unable to retrieve information that was once in long-term memory, it is usually not because the material is lost from long-term memory, but because we don't have enough cues to be able to find it. Let's demonstrate this.

What did you eat for dinner last night?

If you remembered what you ate for dinner last night, this information must have been in your long term memory (because you ate dinner more than 30 seconds ago, and you are still able to remember what you ate). Presumably we have information about every dinner we ever ate somewhere in our long term memories. Usually, however, it is impossible to retrieve that information.

What did you eat for dinner a week ago?

Most people cannot easily retrieve that information. But it is still in your long-term memory. Maybe you can find it if you are given some cues. Think about all the

things you did a week ago. Consult your organizer or calendar if you need to. Where did you eat dinner and who were you with?

Now do you remember what you ate for dinner a week ago?

Once information is in long term memory, it generally stays there. If we can't remember something that is in our long term memory, it generally represents a retrieval problem. Providing additional cues or information can often improve retrieval.

Important point: Retrieval of information from long-term memory is usually easiest if we focus on the meaning of the information both while learning it and while retrieving it.

Important point: The capacity (the number of pieces of information that can be held in memory) of long-term memory appears to be virtually unlimited.

Important point: The duration (amount of time information can be held in memory) of long-term memory appears to be virtually unlimited.

Important point: If you can't remember something you once knew, it is probably a retrieval problem.

Types of Long term Memory:

Research suggests that within long-term memory there are several types of memory. There are several possible ways to divide up long term memory. One way to divide up long term memory is into **implicit memory and explicit memory**.

LONG-TERM MEMORY = IMPLICIT MEMORY + EXPLICIT MEMORY

Explicit memories

These are memories that we can consciously remember. Most of what we commonly consider "memory" is explicit memory. Answers you give on an exam are a product of explicit memory. Everything you "know" you remember as explicit memory. Explicit memory may be further subdivided into **semantic memories** and **episodic memories**. **Semantic memories** are memories about general factual information, such as that George Washington was the first president of the United States. **Episodic memories** are personal, autobiographic memories, such as what your first day of school was like, or what you did on your last vacation.

Implicit memories

These are memories that we do not consciously remember, which nonetheless can be shown to influence our behavior. Since we are not consciously aware of implicit memories, it is difficult to demonstrate that they exist. However, cognitive psychologists have been able to show that memories that we are not aware of are able to influence our behavior. For instance, suppose you were shown 50 photographs today. Then next week you were shown 100 photographs and asked which ones you like best

and which ones you have seen before. You probably won't be able to tell me which ones you have seen before, but there is a good chance that you will "like" the photos you saw a week ago better than those that are new to you. You will not know why this is. This is an example of memories that we are not aware of influencing our daily behavior.

Implicit memory may be further divided into **procedural memory** and **conditioning effects**. **Procedural memories** are memories for how to do things, such as riding a bike or driving a car, while **conditioning effects** are memories that are formed more or less automatically through the processes of classical and operant conditioning.

Implicit and explicit memories seem to be processed and stored in different parts of the brain. The basal ganglia and cerebellum appear to be responsible for implicit memories (there are probably other areas too), while the hippocampus appears to be more responsible for explicit memories.

Patient H. M.

On 23 August 1953, William Scoville performed a bilateral medial temporal lobe resection on patient H. M. in an attempt to stop his epileptic seizures. (The patient's first name is Henry and the surgery was in Hartford, Connecticut). This surgery removed tissue from the **medial temporal lobes including the hippocampi**. The result was a surprise to everyone. After the operation, H. M. experienced a severe anterograde memory impairment that persisted to this day. **That is, he has not remembered anything from the day of his surgery.** Having been studied for more than 40 years, H. M. can be considered the single patient that has provided the largest collection of data to the students of memory.

H. M.'s syndrome is surprisingly isolated. His impairment is mostly limited to his inability to register new facts in his long term memory. That is, he has no ability to consolidate new information into long term stores. This is called a **recent memory deficit**. His IQ is above average. His perceptual abilities are, for the most part, normal. He does not have any attentional disorder. His short term memory is preserved in both verbal and non-verbal tasks. Although his operation was performed when he was 27, his memories are intact until age 16, with an 11 year retrograde amnesia (has lost memories of events and facts that occurred 11 years before his surgery). His language production and comprehension are mostly normal, he can understand and produce complex verbal material

There have been dozens of experiments on H. M.'s memory impairment. In his post-operative years since 1953, his symptoms have been very stable. The major findings show that he is impaired on virtually any kind of learning task in which there is a delay between presentation and recall, particularly if interfering material is presented in between. The learning materials used in tests include photographs of people, verbal material, sequences of digits and complex geometric designs or nonsense patterns. He is severely impaired with his memory of daily life. He does not know, for example, where he lives, who cares for him, what he ate at his last meal, what year it is, who the president is, or how old he is. In 1982, he failed to recognize a picture of himself that had been taken on his 40th birthday in 1966.

More interesting results are the ones that show the tasks that H. M. can perform. For example, the fact that H. M. only has problems with long-term memory but has an intact short term or working memory clearly demonstrates that these two phenomena (long and short term) are supported by different circuitry. Furthermore, the fact that H. M. has intact memories from his childhood, but cannot remember anything new shows that the structures that store memories are separate from the mechanisms that encode them, and the hippocampus probably plays a role in the latter. There are other dissociations discovered on H. M., most notably the experiments on motor and skill learning. In a 1962 experiment, H. M. was trained on a mirror-drawing task. This task involves tracing some figure on the paper by only seeing the mirror image of the drawing. Normal people are initially pretty bad at this task, but they can get better with training. H. M. had a normal learning curve for this task. On later days, even though he denied having performed the task previously, he retained his skill. H. M. was also trained on various other manual tracking and coordination tasks. He showed nearly normal improvement from session to session

Patient R. B.

Remember that the surgery in H.M removed much of the medial temporal lobe lobes including the hippocampi. Patient R.B. had heart bypass surgery and became amnesic after an episode of **global ischemia**. R. B. survived for 5 years and had significant explicit memory deficits. Upon his death histological examination of his brain indicated bilateral loss of cells throughout the CA1 field (Fig. 3) of Ammon's horn. The CA1 field is one of three fields or cellular zones of the hippocampus. There are other adjacent areas such as the dentate gyrus, subiculum, entorhinal cortex and parahippocampal gyrus that were removed in H.M. The **CA1 pyramidal field of the hippocampus is especially vulnerable to the excitotoxic effects of glutamate** that is released during **ischemia**. The study of R. B. is important because it demonstrates that explicit memory loss in humans is possible after damage confined to the hippocampus; .H. M.s lesions were more extensive.

To summarize:

- The hippocampus is not the location of long term memories, nor is it the method of retrieval of these
- The hippocampus is not the location of short term memories, otherwise H.M. would not be able to carry on a conversation
- The hippocampus is involved in converting short term memories to long term memories
- The hippocampus is crucially involved in one of the most important cognitive functions of the brain--memory

An Example

Last night I went home around 6 PM and looked on the front porch and there was a package with a new shirt in it (yeah!). As I looked at the shirt the visual information about the shirt was sent from my visually related cortex to my PFC. At the same time my PFC brought in other long term memories from different cortical areas regarding other shirts and perhaps some comments on them by Med Is. (gee JKH, who chose that combination shirt and tie? Ugh!!). The visual information about the shirt also reached my hippocampus (via the perirhinal cortex) and then my hippocampus in order to enter my long term stores.

After changing my clothes (Levis and a neuroscience t-shirt with level 3!), I fed our yellow lab Toby (dog food and beans!). Then I took the “Tobster” for a walk along the southwest bike path. Of course, I took a plastic bag to pick up his poops (rather generous, so I double bag them!!). As I was walking Toby, I suddenly remembered the new shirt and thought about when to wear it. I brought up this memory from my long term stores and put it on my “black board” or “work bench,” that is, into my working memory.

As I write this in the AM of the following day, I am also bringing the memory onto my black board, as well as other memories about the big poops and the nice spring evening. I also have a few other thoughts in my working memory about what I am hearing on the radio about the NCAA basketball tournament and when my dad took me to see the 1959 NCAA championship game at the University of Kentucky in Lexington (Elgin Baylon played for Seattle). Memory is wonderful!

I hope this helps. Remember, you need to determine if your patients have a deficit in working/short term memory, recent memory, or remote memory.

Table 1. Organization of memory.

<i>Memory systems</i>	<i>Key features</i>
Explicit	Facts & events
	Develops rapidly
	Conscious recollection
Implicit	Skills & habits
	Stimulus-response relations
	Develops slowly
	Behavior is altered unconsciously and expressed through performance

Neural systems involved in implicit memory

Our understanding of the **implicit memory neural system** is not as advanced as the explicit memory system. The available evidence suggests that the cerebellum and the basal ganglia, which consists of the caudate, putamen and globus pallidus, appear to be a major part of this memory system. Information from these brain regions is passed to the VA and VL, which project to premotor and supplementary motor cortical regions. Lesions made in the caudate and putamen of monkeys impaired performance in a task requiring the learning of a habit.

Retrograde amnesia

What lesions might cause retrograde amnesia. Well, consider where the memories of your grandmother are stored. The memories of her face might be stored in assembly of neurons in one cortical area, memories of her voice in another and her gait and her house in other association areas. But your memory of your grandmother is more than just memories of her features. It is the memory of the associations between features,, that is, it is the interconnections (associations) between the assemblies of these neurons, that is critical. The hippocampus establishes these associations. After these associations are established, the activation of one of these areas leads to the activation of others. The sound of her voice triggers a memory of her face, which in turn triggers memories of her house gait, etc. So, to lose these remote memories about your grandmother. This happens where there is a loss of synapses in any of these cortical areas, loss of fibers forming associations between these areas, a lesion of pathways involved in retrieving them into working memory or working memory itself.

Think of the characteristics that define an apple. Sweet and sour, nice smell, hard and crisp, smooth, red, round, grows on a tree, makes a great pie. When we see, touch and smell an apple, a variety of sensory modalities are activated. Each leaves a trace and thus the memories of an apple are scattered over many cortical areas. The job of the hippocampus is to bind of these traces with the same object, an apple. Only after this is done can activity in any one of these pathways directly elicit the memory of an apple

Normal aging and cognition

We often associate aging with dementia and research indicates that as we grow older, brain cells become impaired or disappear. Some of these changes, if they are sufficiently pronounced, undoubtedly impair memory. However, severe deterioration of the brain with age is not an automatic process. Marked deterioration of cognitive functions in older adults is frequently associated with specific diseases such as *Alzheimer's disease*. This section discusses some of the age-associated changes occurring in the brain in relation to cognitive functions.

With increasing age, the brain undergoes a reduction in weight and protein content. This reduction is probably due to the loss of neurons. However, not all regions of the brain are equally likely to lose cells. For example, very few hypothalamic neurons are lost in comparison to cells in the substantia nigra, a major dopamine cell body region, and the locus coeruleus, a major norepinephrine cell body region. Because locus coeruleus cells are involved in arousal functions, loss of these cells may impair the ability to learn complex information. Structures in the limbic system such as the hippocampus also undergo cell death. It is estimated that approximately 20 % of hippocampal neurons are lost during the second half of life. In the cerebral cortex, cell counts decrease with advancing age. Even if neurons survive, their cell bodies, axons and dendrites may atrophy. These alterations are evident in the hippocampus and cerebral cortex, which are regions important for learning, memory, and other cognitive functions. In addition, basal forebrain (esp. nucleus basalis of Meynert) cell bodies and axons projecting to the hippocampus and cerebral cortex undergo

degeneration. These basal forebrain cells secrete the neurotransmitter acetylcholine that plays an important role in memory.

In addition to age-related changes in the **number** and **structure** of **neurons**, internal cellular alterations often occur. In large neurons such as those found in the hippocampus and the amygdala, the bundles of protein filaments known as **neurofibrillary tangles** fill the cytoplasm of cells (Fig. 5). These cytoskeletal elements are made up of poorly soluble hyperphosphorylated isoforms of tau, a microtubule-binding protein that is normally soluble. The relevance of small amounts of neurofibrillary tangles during the **normal aging process** is not known, but brains of humans with Alzheimer's disease contain a **high number** of tangles. The appearance of these neurofibrillary tangles suggests that nerve cells are undergoing alterations that may impair their communication with other neurons.

In aging humans, monkey, and dogs, alterations within the **extracellular space** also begin to appear (between the cells and their processes). In brain regions including the **hippocampus**, **cerebral cortex** and **amygdala**, spherical deposits called **senile plaques** begin to slowly accumulate (Fig. 6). The core of these plaques is formed by aggregates of a small molecule known as **beta-amyloid protein**, which is cleaved from a larger amyloid precursor protein called APP (APP). **APP** is manufactured by our nerve cells but its normal function is not known and how mutant APP causes the death of nerve cells is a mystery. As with neurofibrillary tangles, the functional significance of senile plaques in the normal aging brain is not known but occurs at high densities in brains with Alzheimer's disease.

In general, studies indicate that when elderly people remain in good health, they exhibit only a subtle decline in tests involving memory, perception and language. Subtle changes in cognitive decline are revealed in studies assessing the **speed** at **which new memories** are formed as well as their **retrieval**. The elderly do not encode new information or recall details of a particular event (e.g., place and time; "episodes") as rapidly as young adults. In addition, the more complex a task (e.g., mathematical problem solving) the more likely performance will be impaired. These studies suggest that certain cognitive functions may be associated with the gradual anatomical and physiological alterations that occur in the aging brain.

Some of the functional changes occurring in the aging brain were examined recently using **positron emission tomography** (PET) that measures **cerebral blood flow**. PET scans were made when young (25 years) and old subjects (69 years) were performing tasks in the following order: **memorizing a set of faces** (encoding), face **matching** (perception), and face **recognition**. In the encoding task, subjects were shown 32 unfamiliar faces and asked to memorize them. The face matching task used different faces from the encoding task and required subjects to match a sample face with choice faces presented simultaneously. In the face recognition task, subjects were shown two choice faces in each trial, one of which was unfamiliar, and asked to indicate which face was seen previously from the set of 32 faces. Although there were no age differences in **reaction time**, **accuracy** was **reduced** in **older** subjects, especially in **the face recognition task**.

Cerebral blood flow differed between young and old subjects. In **young** people, **different neural systems** are involved in **encoding** and **recognition**. Face **memory encoding** was associated with increased cerebral blood flow in the **left prefrontal cortex** and **right hippocampus**. **Recognition** was associated with increased activation of the **right prefrontal cortex**. In old subjects, cerebral blood flow failed to increase in the **left prefrontal cortex** and **right hippocampus** during the **encoding** task, but did increase in the **right prefrontal** region during the **recognition** task. These results suggest that **memory impairment** among the **elderly** is due to a lack of **cortical** and **hippocampal** activation leading to insufficient **face encoding** which results in **increased** errors in the **recognition** task.

Aging and Dementia

Dementia refers to a steady decline in cognitive functions such as memory and intellectual skills. As indicated previously, dementia is not an inevitable consequence of aging. However, dementia is related to the aging process. In the United States, approximately **11%** of the population over the age of 65 years suffer from mild to severe forms of dementia (think of your neuro profs). After 75 years of age, the incidence of dementia increases **2%** for each year of life.

It is estimated that **70%** of all reported cases of **dementia** are due to **Alzheimer's** disease. Another **15%** is due to **strokes** and the remaining **15%** are caused by **neurodegenerative** diseases such as **Huntington's** disease and **Parkinson's** disease, or involve conditions that are treatable, e.g., brain infections, endocrine and metabolic diseases, increased intracranial pressure.

The early stages of Alzheimer's disease are marked by **forgetfulness**, **untidiness**, **restlessness**, and brief periods of **confusion** (think again of your neuro profs!). The ability to form new memories (hippocampus), especially regarding time and place ("episodes" in their life) is impaired but memories of the distant past are **less** affected. Some aspects of working memory (PFC) are also affected, especially their digit span (on average, a normal working memory can keep **7** digits on the blackboard without forgetting one). As the disease progresses, patients begin to lose interest in events and eventually become confined to a wheelchair or bed. At the latter stages of the disease, 5 to 10 years after onset, there is a loss of control over body functions and a mental state characterized by mental emptiness.

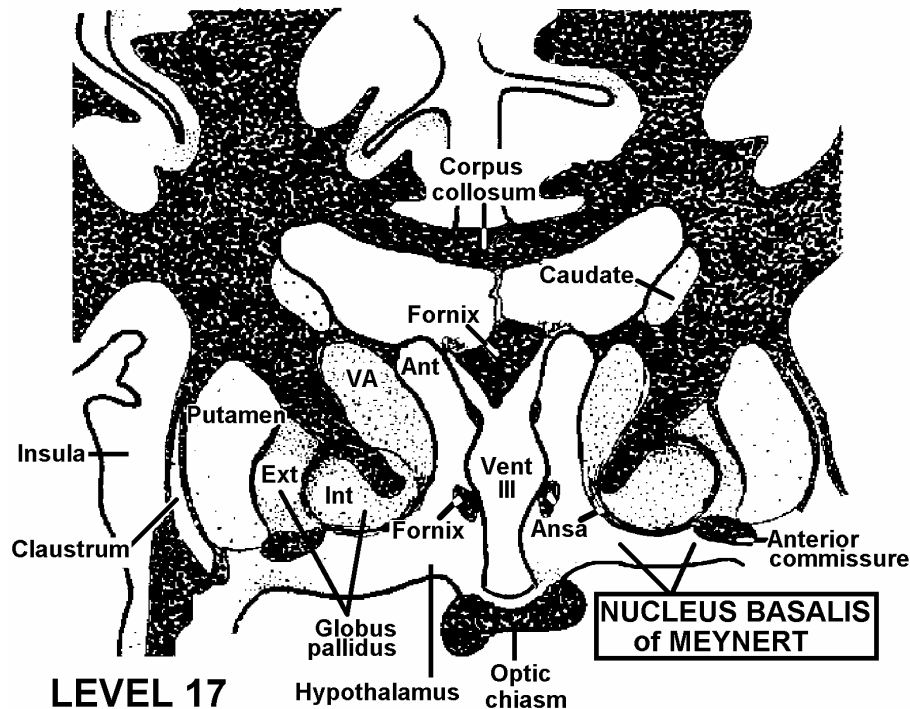
Currently, postmortem examination of the brain provides the definitive diagnosis of Alzheimer's disease. Senile plaques (Fig. 7) and neurofibrillary tangles are the major characteristic neuropathological hallmarks of Alzheimer's disease. Plaques are found scattered throughout the frontal, parietal, occipital and temporal lobes. High densities of plaques are found in the amygdala and hippocampus. **Neuronal cell loss and alterations in neuronal morphology** are also observed in an Alzheimer brain. These brains are reduced in weight and exhibit varying degrees of cortical atrophy in **frontal**, **parietal**, and **anterior temporal lobes**. Neuronal loss is also observed in the **hippocampus**, **amygdala**, the **olfactory system** and in the **nucleus basalis**, a major cholinergic cell

group located in the base of the forebrain. This results in severe cholinergic deficiency in the cortex of Alzheimer's disease patients.

Role of the cholinergic system

In the mid-1970s, researchers reported a striking loss of the **enzyme choline acetyltransferase** in the **hippocampus** and **cerebral cortex** of Alzheimer patients. This enzyme is responsible for the synthesis of acetylcholine and its presence indicates the existence of cholinergic neurons. In humans, **most of the cholinergic fibers** to the hippocampus and cortex originate from neurons in the **nucleus basalis of Meynert** (Fig. 8). These cholinergic cells are located beneath the globus pallidus. The nucleus basalis of Meynert is believed to integrate various subcortical functions important for memory.

In comparison to age-matched controls, patients with Alzheimer's disease exhibit a **severe loss** of neurons in the **nucleus basalis**. That the loss of cholinergic function contributes to the deficits in memory is supported by studies showing that in normal individuals, administration of drugs that **block cholinergic function** produces confusion and **memory disorders**. The cholinergic deficits in Alzheimer's patients have prompted attempts to correct the deficits by giving high doses of cholinergic precursors such as **choline**. In animals, administration of cholinergic precursors produces an increase in brain acetylcholine levels but similar attempts in humans with Alzheimer's disease have not been entirely successful. However, there is currently a drug that **decreases the breakdown** of acetylcholine (an anticholinesterase drug that keeps ACh around longer; called Aricept). In some cases, this drug is effective in ameliorating memory loss associated with Alzheimer's disease. It should be noted that losses **in cortical norepinephrine** activity are also **evident** in the **Alzheimer brain**. Therefore, correcting the imbalance in one neurotransmitter system may not be sufficient to overcome the cognitive deficits induced by loss of other neurotransmitters.



There have been several speculations concerning the cause of the neuronal degeneration in Alzheimer's disease. One speculation is that **neurotrophic or growth factor** activity is **reduced** or the affected neurons become less responsive to these factors. In animal studies, deafferentation (destroying their inputs) of cholinergic neurons leads to neuronal degeneration that is prevented by administration of nerve growth factor. Hence, it may someday be possible to prevent or slow the degeneration of neurons with the administration of neurotrophic factors.

Role of beta-amyloid protein

Research directed at understanding the bases of the beta-amyloid deposits have pointed to genetic mutations as a molecular cause of Alzheimer's disease, at least under some circumstances. Studies indicate that a mutated gene is associated with an increase in amyloid precursor protein (APP). This precursor is made by most cells in the body but its normal cellular function is unknown. Cell culture studies suggest that some forms of APP regulate cell growth and the length of dendrites and axons. β -amyloid protein is produced after it is cleaved from the larger APP by enzymes. The mutated gene, however, potentiates extracellular and vascular deposition of the β -amyloid protein. Depending on the mutation, the level of β -amyloid protein produced will vary. This variation in deposition rate may explain why differences exist in the onset and course of the disease.

A major breakthrough came with the discovery that the APP gene is located on chromosome 21. This finding provided insight into why individuals with Trisomy 21 syndrome (these individuals have an extra copy of chromosome 21) develop β -amyloid plaques from an early age. Postmortem brain examination of Trisomy 21 patients that died early in life indicate that a few β -amyloid protein deposits already exist during the teenage years, and by their twenties and thirties Alzheimer's like dementia is manifested. By the fourth and fifth decades of life, the Trisomy 21 patient has high brain concentrations of senile plaques and neurofibrillary tangles accompanied by severe dementia. These results suggest that the mutation-induced production of β -amyloid plaques contributes to the onset of some cases of Alzheimer's disease.

Investigators, however, have long-suspected that all forms of Alzheimer's disease are not due entirely to a mutation on chromosome 21. The common sporadic form of the disease generally strikes after age 65 whereas other early-onset forms appear at earlier ages. Recently, researchers have discovered two additional genes linked to Alzheimer's disease. One gene was found on **chromosome 14** and is responsible for 80% of the cases of **familial Alzheimer's** disease, a virulent form of the disease that strikes as early as age 40. The other discovered gene that appears to be closely related to the chromosome 14 gene, is found on **chromosome 1**. It is suspected that mutations of both genes leads to excess β -amyloid production. These findings indicate clearly that Alzheimer's disease is a **genetically heterogenous disorder**.

It is currently not known how the protein produces its effects on cell bodies, axons and dendrites. What is clear is that the gradual accumulation of β -amyloid protein in conjunction with **neurofibrillary tangles**, leads to a degeneration or disconnection of neuronal systems that critically underlie memory and other intellectual functions. Over time, limbic structures are no longer able to communicate with neocortical and other brain regions, leading to the inevitable decline in memory, judgment and language.

Problem Solving

1. Explicit memory:
 - A. develops slowly
 - B. is more likely to be disrupted by hippocampal lesions
 - C. are consciously recalled
 - D. is activated by performance
 - E. two of the above are **TRUE**

2. The nucleus basalis of Meynert:
 - A. contains cells that secrete NE
 - B. injection of anticholinesterase drugs decrease amounts of ACh in the hippocampus
 - C. undergoes a marked loss of cells in the Alzheimer brain
 - D. is located in the brain stem
 - E. two of the above

3. Which one of these statements is **FALSE**?
 - A. a patient with hippocampal damage will be able to hold a telephone number in their mind
 - B. a patient who sustained bilateral hippocampal damage today will remember what he/she did last week
 - C. a patient who sustained bilateral hippocampal damage today will have difficulty learning a new motor skill in the future
 - D. a patient with plaques and tangles in their medial temporal structures may not be able to recognize the face of someone they met last week
 - E. a patient who sustained bilateral hippocampal damage today could relate details of what he/she did last week

4. A monkey with bilateral damage to the hippocampus:
- A. has working memory
 - B. could do “mental arithmetic”
 - C. would show fear when shown a snake (if raised in the wild)
 - D. would be abnormally aggressive
 - E. A, B, and C
5. Which of the following characteristics are **TRUE** about the normal aging brain:
- A. hypothalamic cell loss, loss of cholinergic neurons from nucleus basalis, loss of hippocampal neurons
 - B. brain weight reduction, hypothalamic cell loss, neurofibrillary tangles
 - C. locus ceruleus cell loss, brain weight reduction, neurofibrillary tangles
 - D. hippocampal cell loss, loss of cholinergic neurons from nucleus basalis, senile plaques
 - E. two of the above are TRUE
6. Damage to the CA1 region of Ammon's horn (part of “hippocampus”) is likely to produce:
- A. deficits in implicit memory
 - B. anterograde amnesia
 - C. deficits in working memory
 - D. patient would not remember first crush (patient is 62 and had the crush in the second grade)
 - E. inability to learn a motor skill
7. The patient R.B., who could not form new memories, had damage in:
- A. CA3 region of hippocampus
 - B. basal nucleus of Meynert
 - C. a wide expanse of hippocampus
 - D. CA1 region of hippocampus
 - E. basal ganglia and amygdala
8. Implicit memory:
- A. performance is measured by doing a task versus recalling a prior experience or fact
 - B. is acquired in the absence of conscious awareness
 - C. is acquired slowly
 - D. involves the caudate and putamen
 - E. all the above

9. Which of the following statements is **TRUE**?
- A. if a bell is always associated with the presentation of food, the bell will eventually cause salivation: this is an example of explicit learning
 - B. a monkey with bilateral damage to the amygdala will not exhibit fear conditioning
 - C. a monkey given high doses of amphetamine may appear to hallucinate
 - D. a human with damage to the hippocampus is likely to forget all old memories
 - E. two of the above are true
10. Which of the following associations is/are **TRUE**?
- A. working memory - hippocampus
 - B. explicit memory - basal ganglia
 - C. implicit memory - PFC
 - D. neurofibrillary tangles - cytoskeleton
 - E. senile plaques - cytoskeleton
11. Which of the following statements is **FALSE** regarding the aging brain?
- A. brain cells become impaired or disappear
 - B. reduction in weight and a decrease in protein
 - C. NE cells in nucleus basalis die
 - D. neurofibrillary tangles are found
 - E. senile plaques are found
12. Brains of Alzheimer's patients:
- A. have senile plaques within the cytoskeleton, and loss of synapses in cortex
 - B. have neurofibrillary tangles, the cores of which are comprised of β -amyloid protein
 - C. have neurofibrillary tangles in the cytoskeleton
 - D. are affected only in the hippocampi
 - E. are most affected in the visual cortex, especially Meyer's loop
13. Which of the following statements is **TRUE**?
- A. the duration of short term memory is 3 hours
 - B. R.B.'s lesion was larger than H.M.'s
 - C. cortical levels of acetyl choline are normal in the Alzheimer brain
 - D. a neurotrophic factor could play a role in Alzheimer's
 - E. none of the above is TRUE

14. Which of the following statements is **TRUE**?
- A. the amyloid precursor gene is located on chromosome 12
 - B. young trisomy 21 patients exhibit β -amyloid protein deposits
 - C. chromosome 21 is implicated in familial Alzheimer's disease
 - D. Alzheimer's disease is a genetically homogeneous disorder
 - E. two of the above are **TRUE**
15. H.M. had both hippocampi removed and has a **recent memory** deficit. Which of these statements is/are **TRUE** about him following his surgery?
- A. can make notes regarding what he just has read
 - B. can carry on a conversation, as his language skills were
 - C. can learn new sports skills but will not remember that he has ever played the sports
 - D. can remember his name and childhood
 - E. all of the above are **TRUE**
16. H.M. had both hippocampi removed and has a **recent memory** deficit. Which of these statements is/are **TRUE** about him following his surgery?
- A. remembers books he has read (since surgery)
 - B. finds re-reading a novel boring, as he remembers the surprise ending (like the Neuro course book!)
 - C. when watching TV, can't remember the faces of the actors from scene to scene
 - D. can remember the route to his new house
 - E. can recognize his face in the mirror

PROBLEM SOLVING ANSWERS

- | | |
|----------------|-------|
| 1. E (B and C) | 14. B |
| 2. C | 15. E |
| 3. C | 16. C |
| 4. E | |
| 5. E (C and D) | |
| 6. B | |
| 7. D | |
| 8. E | |
| 9. E (B and C) | |
| 10. D | |
| 11. C | |
| 12. C | |
| 13. D | |