Introduction to Brain and Behaviour
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Lecture – 23
The Medial Temporal Lobe Memory System

Hello and welcome to the course Introduction to Brain and Behaviour. I am Doctor Ark Verma from IIT Kanpur. This is the fifth week of the course and we are talking about the medial temporal lobe memory system. Now, if you remember in the last lecture I showed to you the entire structure of the medial temporal lobe with it is various parts that are supposed to be very very important in various aspects of memory. We will talk about the same to a little bit more detail in today's lecture.

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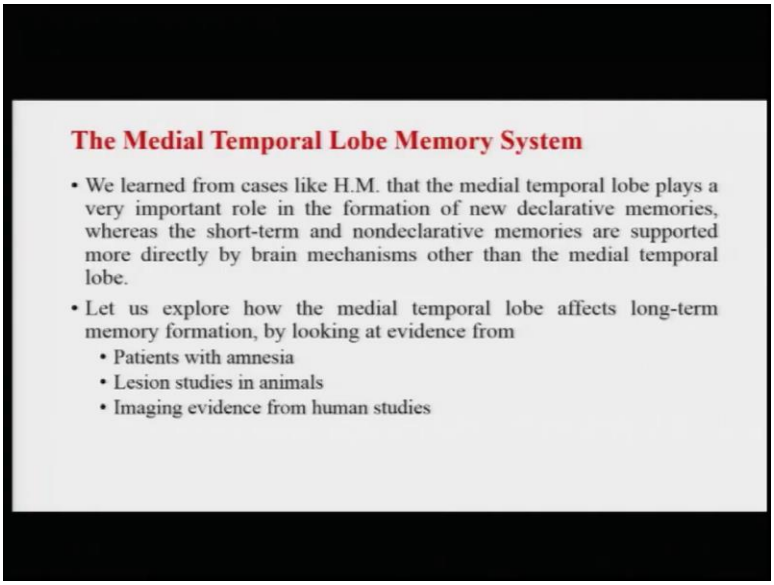

Now, we have learnt from cases like the case of H.M. Henry Molaison that the medial temporal lobe plays a very important role in the formation of new declarative memories whereas the short-term and non-declarative memories are supported more directly by brain mechanisms other than the medial temporal lobe structures. So, we sort of kind of we got this idea from the patients studies that we have reviewed so far.

Now, how does the medial temporal lobe actually effect a formation of long-term memories lets look at that and we basically look at three kinds of evidence patients with amnesia, lesion studies with animals and imaging evidence from the human studies. In today's lecture we will cover

evidence from the first two points and in the fourth lecture of the week we will talk about imaging evidence from human studies.

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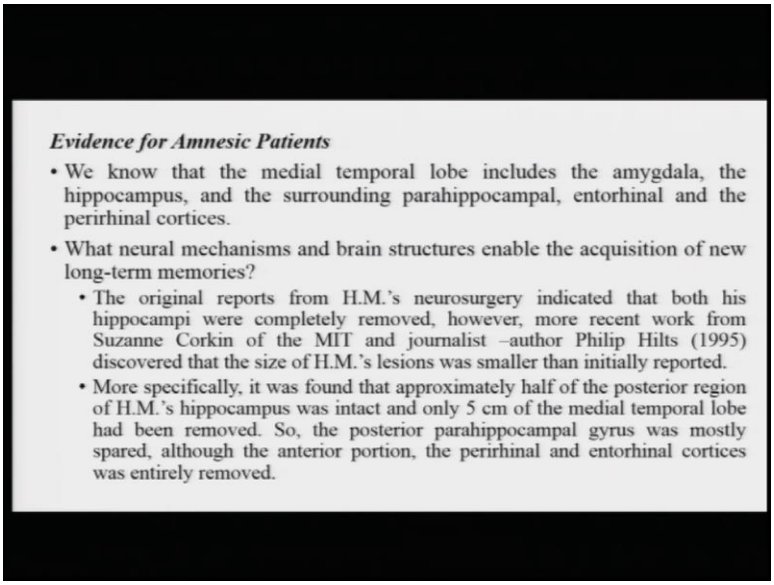

Now let us talk about amnesic patients. We know that the medial temporal lobe includes structures like the amygdala, the hippocampus, the surrounding parahippocampal, entorhinal and the perirhinal cortices. Now, we can ask, what are the neural mechanisms and what are the brain structures that enable the acquisition of new long-term memories?

So, this is a very relevant question. This is a very important question that memory researchers have been struggling through and memory researchers have been trying to find their way around on it. So, just to sort of answer those questions let us go back and let us look at the reports that came the neurosurgical reports of H.M. and let us see if there are any new insights to learn from there.

Now, the original report from the H.M.'s neurosurgery indicated that both of his hippocampi from the left and the right hemisphere respectively were completely removed, however more recent investigations by Suzanne Corkin of the MIT and another journalist Philip Hilts discovered that actually the size of H.M.'s lesions were much smaller than were initially reported.

More specifically, it was found that approximately half of the posterior region of H.M.'s hippocampus was intact and only about 5 cm as compared to the 8 cm that was initially reported

of the medial temporal lobe had been removed. So, basically it tells us what probably was intact was a slightly more larger area than was initially believed. However, the posterior hippocampal gyrus was mostly spared, although the interior portion that is the perirhinal and entorhinal cortices were completely removed. So, this sort of came as a new profile of H.M.'s injury which was basically studied using fMRI etc.

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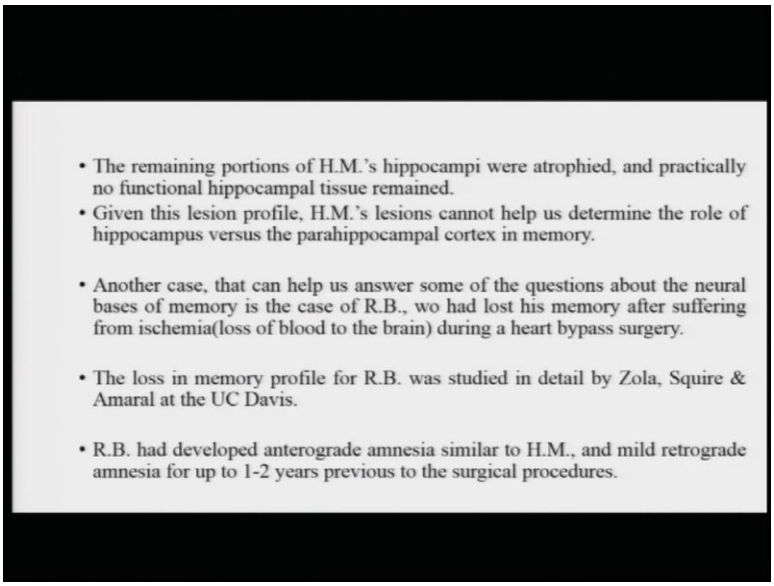

Now, if you kind of look slightly more closely however the remaining portions of H.M.'s hippocampi were actually atrophied. And therefore practically no functional hippocampus tissue actually remained. So, given this lesion profile, H.M. will not be the ideal patient or H.M.'s lesions will not really be informative to us about the role of the hippocampus versus the role of the parahippocampal cortex in memory formation.

So, we need to kind of look at some other cases, some other patient profiles that will sort of give us this contrast of what does the hippocampus do versus what does the parahippocampal cortices contribute. A similar case basically could be of this patient called R.B. who had actually lost his memory after suffering from ischemia which is basically a temporary loss of blood to the brain during a heart bypass surgery.

The loss in the memory profile for R.B. was basically studied by Zola, Squire and David Amaral at University of California Davis. Now, let us look at the deficits he had. R.B. had actually

developed an anterograde amnesia similar to H.M. and a mild retrograde amnesia for up to 1 to 2 years previous to the surgical procedures. So, which is slightly similar to H.M.'s profile.

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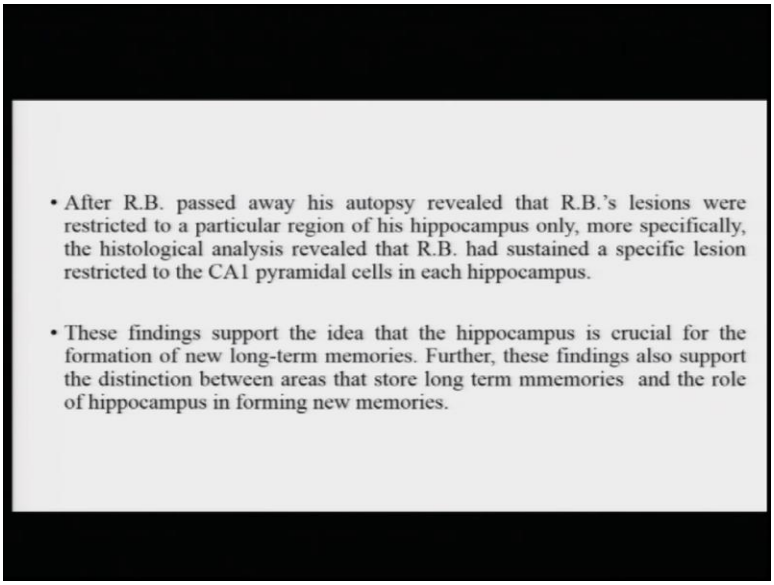

After R.B. had passed away his autopsy revealed that R.B's lesions were actually restricted to a very specific region of the hippocampus. More specifically, the regions that were effected in R.B. were basically the CA 1 pyramidal cells in each of the 2 hippocampi. Now, these findings support the idea that the hippocampus is crucial for the formation of new long-term memories.

Further these findings also support that the distinctions between areas that store the long-term memories and the hippocampus in forming new. So, there are different areas that are basically storing these long-term memories and other areas and basically this ascertains the role of the hippocampus in the formation of new memories.

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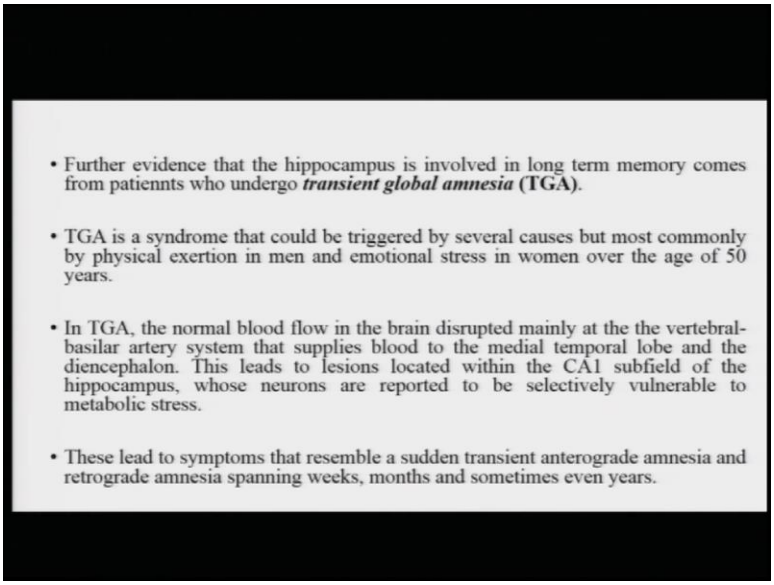

More evidence about the role of the hippocampus in the formation of new long-term memories comes from patients who suffer from this symptom called or disease called transient global amnesia. Now, transient global amnesia is actually a syndrome that can be triggered by several causes but is most commonly triggered by physical exertion in men and emotional stress in women who are over 50 years of age.

In transient global amnesia, the normal flow of the blood is disrupted at the vertebralbasilar artery system and this is a system that actually supplies the blood to the medial temporal lobe and between the diencephalon. So, when the blood supply here is disrupted, these lesions basically it leads to lesions located within the CA 1 subfield of the hippocampus, the same region that we saw was atrophied in R.B.

And the neurons here are supposed to be selectively vulnerable to metabolic stress. So, when these areas are when the blood supplies in this area is disrupted for a while and the neurons in this specific CA 1 subfield of the hippocampi are damaged this is what probably triggers or say for example can be attributed to cause the line of symptoms that we will see in transient global amnesia. So, we just have to remember that.

Now, what are the symptoms in transient global amnesia? Symptoms basically resemble as sudden transient anterograde amnesia and retrograde amnesia that could span weeks, months,

sometimes even years. So, both anterograde and retrograde memory are affected in transient global amnesia.

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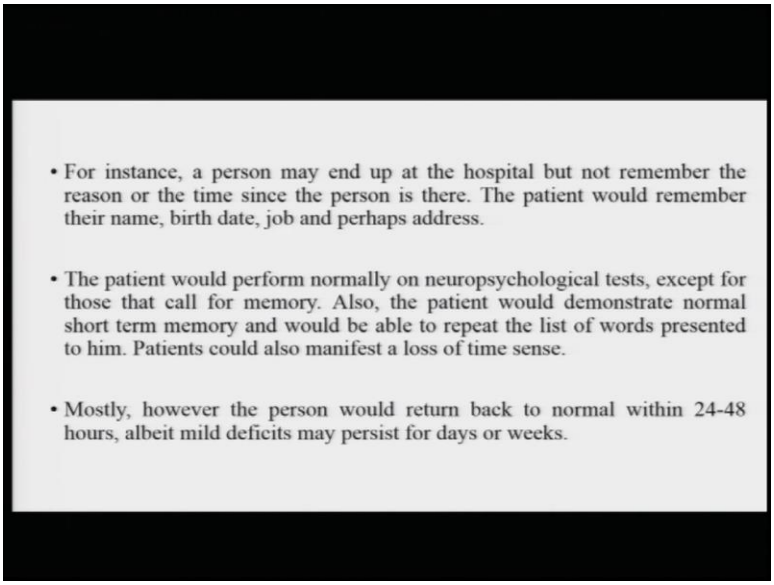

For instance a person may end up at the hospital but not really remember why have they come to the hospital and when did they come there and how did they land up there. The patients would sometimes remember basic knowledge such as their name, their birth date, their job, sometimes even their addresses but they will not really remember how they have landed in that situation.

Also these patients would normally perform perfectly alright on several neuropsychological tests, except for tests that call for memory to be recruited. So, the patient would be able to demonstrate normal short term memory and would also be able to repeat a list of words if it were presented to him.

Finally the patient would also manifest a loss of time sense. So, temporal orientation is sort of disturbed. Finally what happens in transient global amnesia is the person most typically would return back to normal within 24 to 48 hours, albeit mild deficits that might persist for a few more days or few more weeks.

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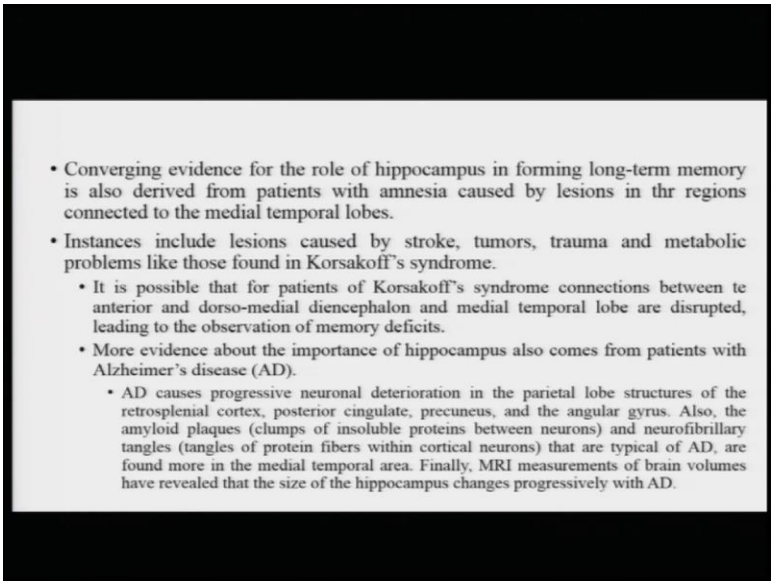

Now, converging evidence for the role of hippocampus in forming long-term memories is also or can also be derived from patients with amnesia caused by lesions in other regions that are connected to the medial temporal lobes but may lie outside of them. For example lesions caused by strokes, tumors, trauma and other metabolic problems say for example, like those found in the Korsakoff's syndrome.

I hope you remember what Korsakoff's syndrome is like. Korsakoff's syndrome is basically a syndrome where participants experience amnesia or loss of memory on account of heavy alcoholism. Now, it is possible that patients who are suffering with Korsakoff's syndrome basically what that happens is the connection between the anterior and the dorso-medial diencephalon and the medial temporal lobe are disrupted and which basically leads to the observation of memory deficits.

More evidence about the importance of hippocampus also comes from profiles of patients who suffer from the Alzheimer's disease. Now, Alzheimer's disease causes progressive neuronal deterioration in the parietal lobe structures of the retrosplenial cortex, the posterior cingulate cortex, the precuneus and the angular gyrus.

Also the amyloid plaque and the neurofibrillary tangles that are typically found in AD patients are found congriated more in the medial temporal lobe area and not really distributed throughout the brain. Finally, MRI measurements of brain volumes have also revealed that the size of the

hippocampus reduces or changes progressively with deterioration with respect to Alzheimer's disease. So, this is typically the region which is getting affected and it is causing the memory deficits or the deficits that are typical of Alzheimer's disease as well.

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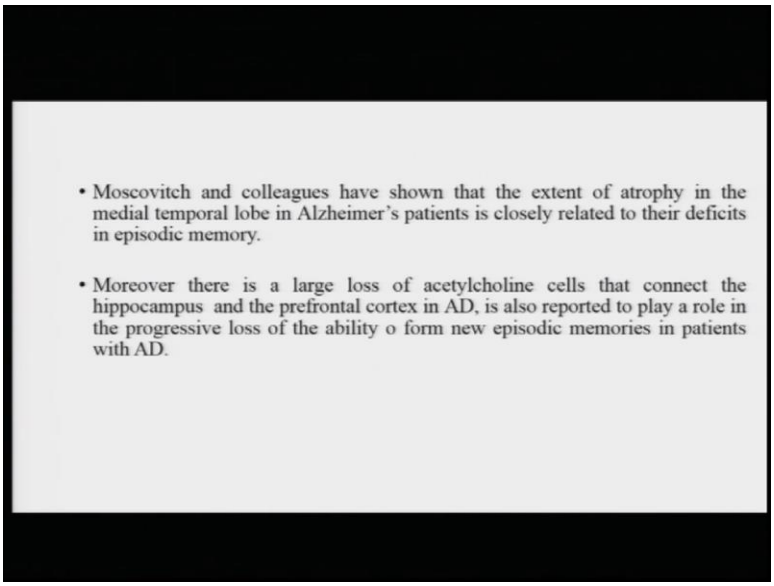

The Moscovitch and colleagues actually have shown that the extent of atrophy in the medial temporal lobe in Alzheimer's patients is very closely related to their deficits in episodic memory. So, medial temporal lobe in that sense and hippocampus in particular can be linked with loss of memory in Alzheimer's patients as well.

There is moreover in addition to atrophy, there is a large loss of the acetylcholine cells that connects the hippocampus and the prefrontal cortex in Alzheimer's patients. This loss of acetylcholine cells is reported to play a role in the progressive loss of the ability to form new episodic memories in patients with Alzheimer's disease.

So all in all we can see that through several sources these evidence can be collected that implicate the medial temporal lobe in general and the hippocampus in particular for the formation of new long-term memories.

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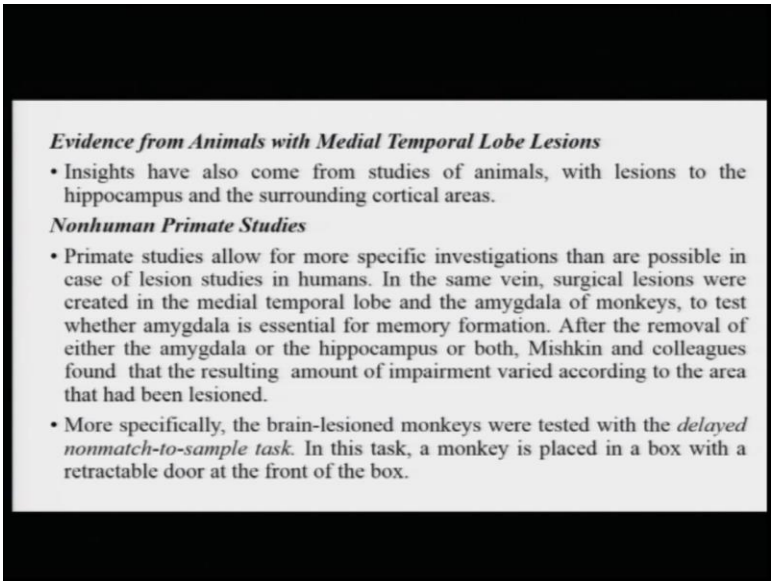

Now lets look at some evidence that comes from the studies of animals who have medial temporal lobe lesions. Now let's first look at non-human primate studies. Now, primate studies obviously allow for more specific investigations than are possible in case of lesion studies with humans. See with humans you cannot really create lesions suited to your experimental hypothesis or to be able to test what specific questions you want to ask.

However on the other hand in non-human primate studies you can also create things like surgical lesions and can actually measure the deficit or the loss that is experienced in response to the lesions that you are made.

Let us look at some of the studies in the same way. Now, surgical lesions were created in the medial temporal lobe and the amygdala of monkeys to test whether amygdala is necessary for memory formation. After removal of either of the amygdala or the hippocampus or both the amygdala and the hippocampus, Mishkin and colleagues found that the resulting amount of impairment varied according to the area that had been lesioned.

So, the amount of area that had been lesioned was correlated with the amount of memory deficits these monkeys were experiencing. More specifically however when the brain lesioned monkeys were tested with the delayed nonmatch-to-sample task new findings emerged. Let us look at what are nonmatch-to-sample task is. In this task the monkeys placed inside a box with a retractable door at the front of the box. So, the monkey is kept in a cage. There is a door. Once

you close the door the monkey cannot see outside of the cage. Once you open the door the monkey can see outside of the cage and even in sometimes it can kind of put its hand forward to manipulate and touch stay with it.

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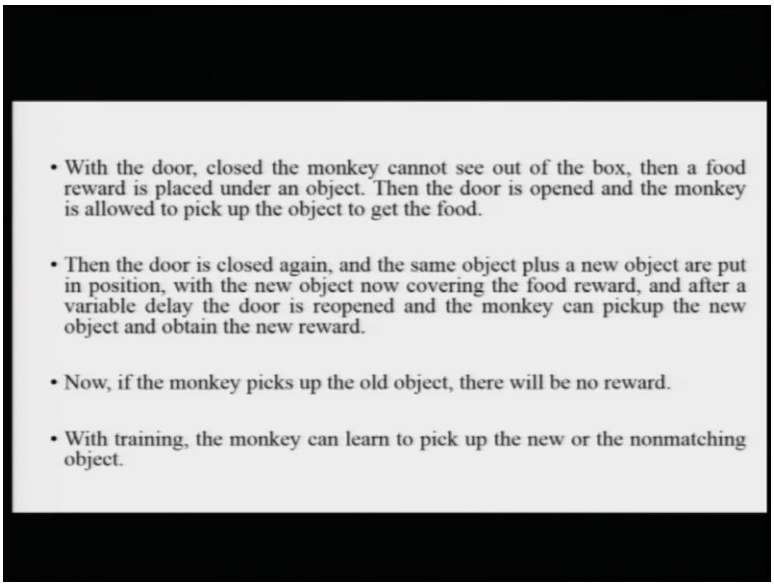

Now, when the door is closed as I said the monkey cannot see outside of the box then a food reward is placed under a particular object. Let us say for example you can keep a cup and a jug. You have placed a food reward under a cup. Then the door is opened and the monkey is allowed to pick up the cup and pick up the object and get the food.

Then the door is closed again and the same object plus a new object, so first time you just kept the cup. Second time you can keep a cup as well a glass or a jug, you can present the same object and this time what you will do is that the new object will be now covering the food reward. So, initially the monkey had just lifted the cup, taken the food and gone back. This time when the monkey opens the door or when the door is opened you can see that there is a cup and there is a glass. This time the food is under the glass.

So, the monkey will have to remember where did he you know find the food in the last trial. Now, if the monkey will pick up the old object there will be no reward. With training the monkey will realise that okay everytime this is done, the food is found to be in the new object. So, basically this is what is called a nonmatching object, object which does not match the presentation in the previous trial. So, with practice the monkey actually realises that this is what

is happening. Every time once I have taken the food and the door is opened again the food will have changed its location to the new object. So, this is a very very simple task.

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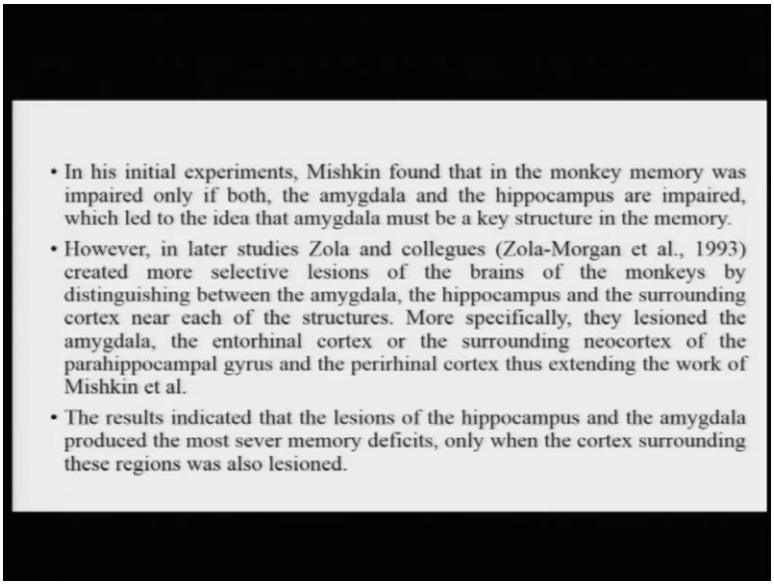

Now, in the initial experiments Mishkin found that in the monkey memory was impaired only if both the amygdala and the hippocampus are impaired which led to the idea that amygdala might be really important structure in memory. However, in the later studies Zola and colleagues created more selective lesions of the brains of the monkeys by distinguishing between the amygdala, the hippocampus and the surrounding parahippocampal cortices near each of the structures.

More specifically, they lesioned the amygdala, the entorhinal cortex or the surrounding neocortex of the parahippocampal gyrus and the perirhinal cortex and thus trying to extend the work of Mishkin and colleagues. What they found was interesting. So, the results indicated that the lesions of the hippocampus and the amygdala produced the most severe memory deficits only when the surrounding cortex was also lesioned.

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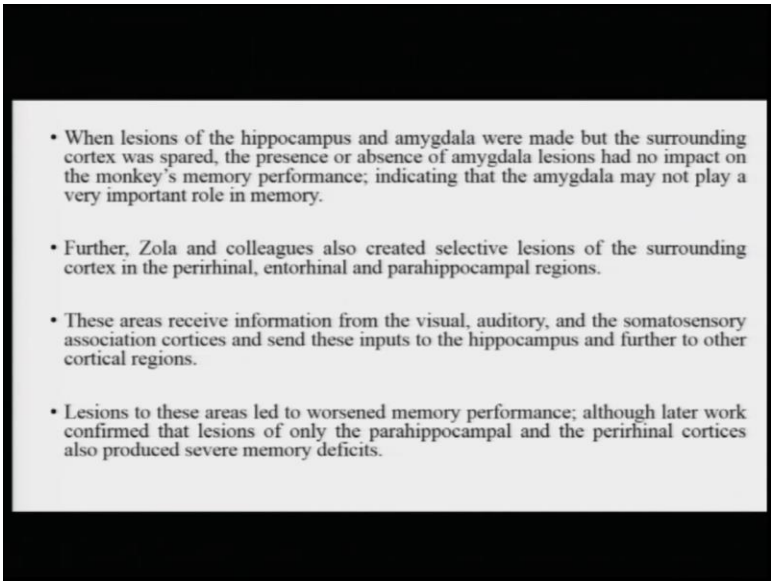

If the surrounding cortex was not lesioned then the presence or absence of amygdala lesions did not have any impact on the monkeys memory performance. This indicates that the amygdala in fact was not really playing a very important role in formation of memories. In fact the surrounding cortex the surrounding parahippocampal cortex, the entorhinal and the perirhinal cortices were playing a more important role in formation of new memories.

Moving further Zola and colleagues also created selective lesions of the surrounding cortex that is the perirhinal, entorhinal and the parahippocampal regions. These areas receive typical information from the visual, auditory and somatosensory association cortices and send these inputs to the hippocampus and further from there to other cortical regions.

Now, when lesions were made to these areas they led to worsened memory performance. Although later work confirmed that lesions of only of the parahippocampal and the perirhinal cortex actually caused severe memory deficits. So, we have to see within the hippocampal region other than the hippocampus these surrounding areas like parahippocampal and the perirhinal cortices are also very very important players in formation of new long-term memories.

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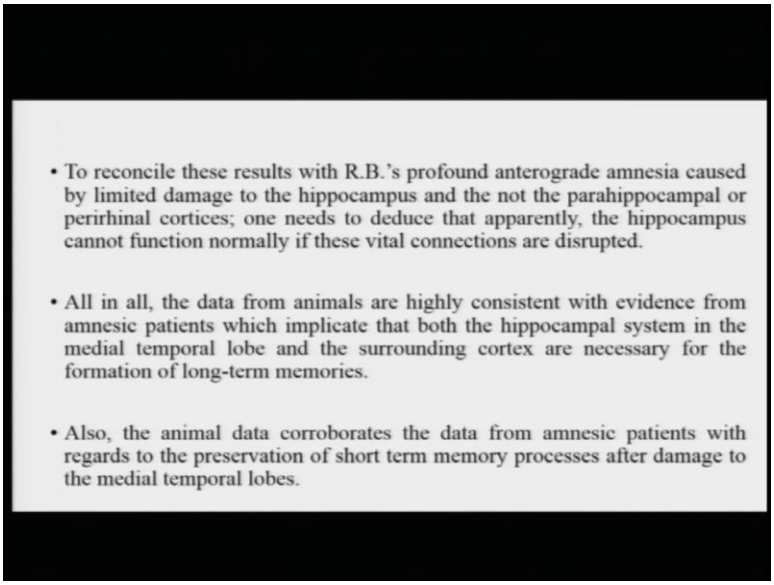

Now, to reconcile what is found through these non-human primate studies with these monkey studies with what we have got through the profile of R.B. basically we can actually say that the anterograde amnesia cause basically R.B. with by just limited damage to the hippocampus and not the parahippocampal and perirhinal cortices.

One needs to deduce that apparently the hippocampus will not be able to function normally if those vital connections are disrupted. So, what had happened in R.B.? R.B.'s profound anterograde amnesia was caused by damage just to the hippocampus and not the surrounding parahippocampal, perirhinal cortex.

However, if these cortex are damaged the hippocampus will not be able to function properly and therefore the patient will suffer from this kind of anterograde amnesia. Now, if you look at all of these together data from animals are highly consistent with the evidence from amnesia patients which implicate both the hippocampal system in the medial temporal lobe and the surrounding cortex as necessary for the formation of long-term memories. So this is something that you have to remember.

Also the animal data basically corroborates the data from amnesic patients regarding the preservation of short-term memory processes after damage to the medial temporal lobes. So, in case the medial temporal lobes are lesioned, short-term memory formation and maintenance functions rather smoothly.

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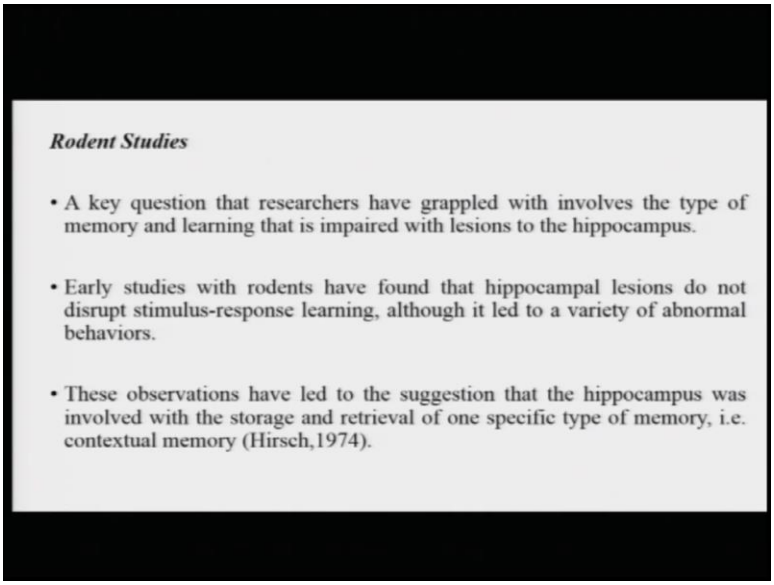

Now, let us talk about final studies, rodent studies. Now, rodent studies have been very important source of insights about the mammalian brain and therefore they also occupy very important place in the animal studies. Let us look at key question now. A key question that researchers have having grappling with or having grappled with involves the type of memory and learning that is impaired with lesions to the hippocampus. What is the type of memory that gets damaged if initially earlier talked about different types of memory you remember, explicit memory, implicit memory, procedural memory you know those kinds of things.

What is the type of memory that gets damaged when the hippocampus is lesioned? Now, early studies with rodents have found that hippocampal lesions do not disrupt things like stimulus response learning although it can lead to a variety of other kinds of abnormal behaviours. So, these observations have led to the suggestion that hippocampus was actually involved in the storage and retrieval of one very specific type of memory that is contextual memory, the memory with context. Say for example, if an event was happening. Where the event was happening?

Who all are involved? What is this situation? That is the context and they are sort of rodent studies are implicated. The hippocampus as being responsible for contextual memory. Now, for example let us see how they have done it.

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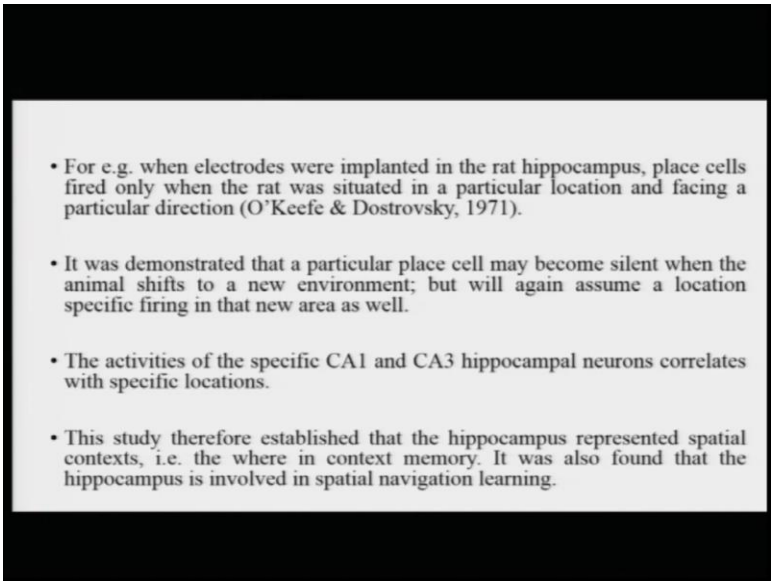

For example, when electrodes were implanted in the rat hippocampus, place cells fired only when the rat was in a particular location and facing a particular direction. So, exactly the same coordinates in space. Only then the place cells in the hippocampus were firing. It was demonstrated that a particular place cell if may become silent, if you move the rat to a different environment but later it will start firing with respect to that specific ambience those specific special coordinates as well. Now, the activity is of the specific CA1 and the CA3 hippocampal neurons have also been found to correlate with specific locations.

So, what does this tell us? It tells us that the hippocampus as a region of the brain represents the special context. It represents where exactly in the contextual memory or where exactly a particular event is taking place. It was also found that the hippocampus is involved in what is called a spatial navigation learning. Let us look at that in some detail.

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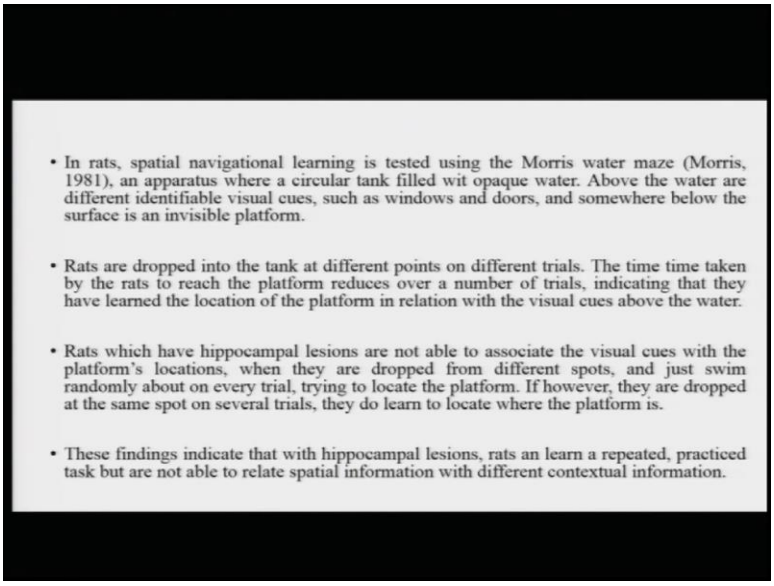

Now, in rats spatial navigational learning is tested using the Morris water Maze task involves a very nice apparatus where a circular tank is filled with opaque water. It is coloured water. So, you cannot see down to the bottom of the tank from the top of the tank. So, what happens is above the water there are different identifiable visual cues such as windows or doors etc. And somewhere below this opaque surface of water there is an invisible platforms.

So, that is the Morris water maze apparatus. Now, rats are dropped into the tank at different points on different trials. So, different places. Suppose this was the tank. Sometimes you drop him here. Sometimes you drop him here. Sometimes you drop him here. So, the rats are dropped into the maze at different points across different trials and the times that the rats take to reach the platform it is seen that this time reduces over a number of trials.

So, what might be happening? With time the rats are learning to locate the platform with respect to the initial position that they were dropped in. So, they are kind of making this relations that okay this is where near this window I was dropped and from here if I move in this direction this is how we will reach the platform. So, they are basically using the visual cues from top of the surface of the water as reference points.

Now, rats which have hippocampal lesions were found that they are not able to associate with the visual cues with the platforms locations and so whenever they were dropped from the water from different spots they would just start swimming randomly and looking for the platform. However,

if these rats were dropped again and again from the same spot at the exact same location they gradually learn to find out where the platform is. Now, what do you make of these findings?

These findings indicate that rats with hippocampal lesions rats can learn a repeated practice task but they are not really able to relate spatial information with different contextual information. Suppose you drop from point A versus point B versus point C, the rats are not being able to use these points as reference to reach the platform when they have these hippocampal lesions.

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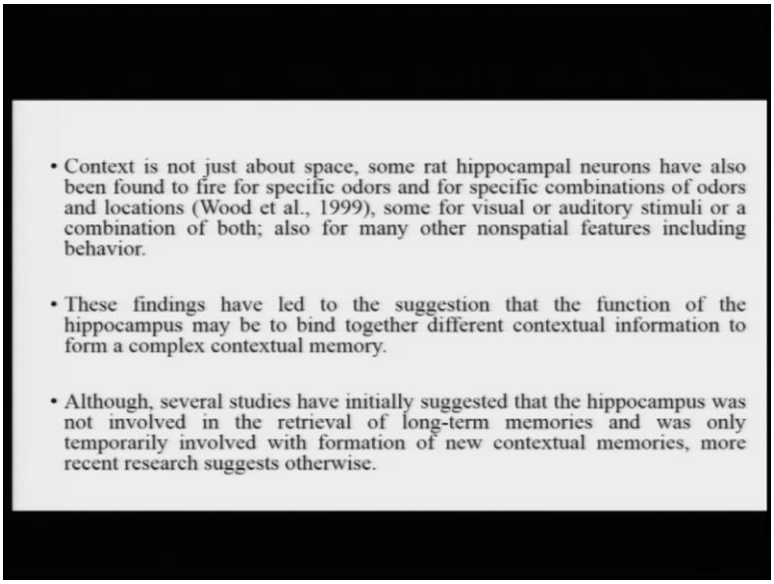

So, that is something which is very important. Now, context is not just spaces, not just all about exact space or exact spatial coordinates. Some rat hippocampal neurons have also been found to fire for very specific odors or for specific combinations of odors and locations. Some rat hippocampal neurons have also been found to fire for visual or auditory stimuli or a combination of visual and auditory stimuli and also for many other kinds of nonspatial features including different kinds of behavior.

Now, what does this tell us? It tells us there is this system in the rats hippocampus or probably ours as well because you know we are also very sensitive to specific ambiances. We are also very sensitive to say for example, when you enter the mess of your canteen then you enter the mess of your hostel, there is a very specific odor. There is a very specific smell that is associated with.

So, even if you are kind of blindfolded and somebody lands you inside the mess you will automatically recognize this is where I am. Sometimes say for example particular rooms in your house have a particular characteristics smell because say for example, if there is a you know place of worship inside there or if there is a particular kind of a perfume kept there.

So, we are also sort of sensitive to these kinds of things and which is basically seen in the rats hippocampus as well. Now, if you look at these findings, these findings have led to the suggestion that the function of the hippocampus may be to bind together different kinds of contextual information and enable the formation of a very complex contextual memory. So, what the hippocampus might be doing is that it is combining different sorts of contextual information with the information of the exact event and then forming a very complex contextual memory.

So, it is not like what did I eat in lunch. It will also be, where did I eat it? Who served it? What was the aroma like? What was the ambiance like? Was there music? Was there no music? Was there a nice view? Was there not a nice view? All of that information will be bound together at the level of the hippocampus and a complex contextual memory will be created.

Although several studies have initially suggested that the hippocampus was not involved in the retrieval of long-term memories and was only temporally involved in the formation of new contextual memories, more recent research sort of suggest otherwise. So, we will talk about that.

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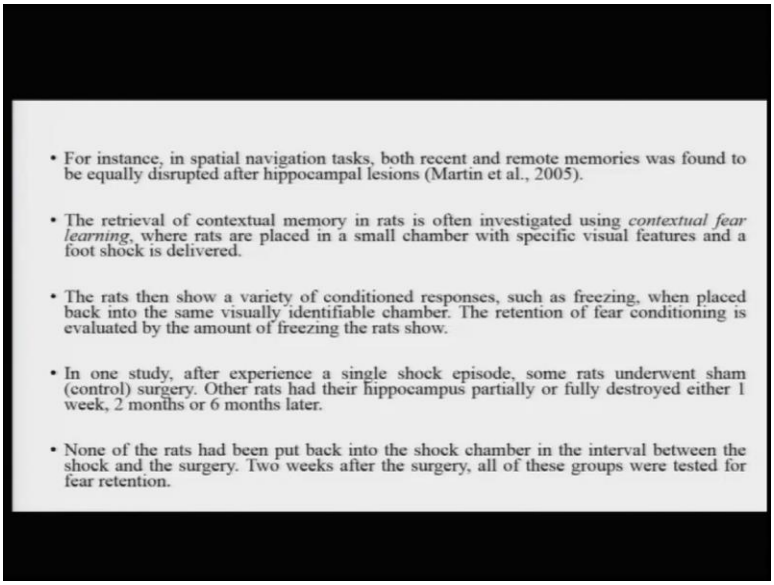

Now, for instance, in spatial navigation task both recent and remote memories were found to be equally disrupted after hippocampal lesions. For instance, the retrieval of contextual memory in rats often investigated using contextual fear learning. So, for example here what happens is that the rats are placed in a small chamber with very specific visual features and a foot shock is delivered.

So, for example in a particular chamber which has let us say let's imagine there is a room with a particular painting and as soon as the rat enters the particular room with that specific painting a foot shock is delivered. Now, the rats can then show a variety of conditioned responses such as they would freeze on entering into that room.

The retention of fear conditioning is evaluated by the amount of freezing that the rats would show. Whether they will completely freeze because they are almost reliving that experience of getting that foot shock. Now, in one of these studies, after a single shock episode some rats underwent a sham surgery.

So, if they just control in a surgery that thing was actually done. Other rats had their hippocampus partially or fully destroyed and either week, 2 months or 6 months later. So, the testing then was supposed to be done week later or 2 months later or 6 months later. Now, none of the rats had actually been put back into the shock chamber in the interval between the shock and the surgery, 2 weeks after the surgery all of these groups were tested for fear retention whether they remember the same visually identified chamber whether they be freeze in response to that chamber or not. So, this is something that was supposed to be tested.

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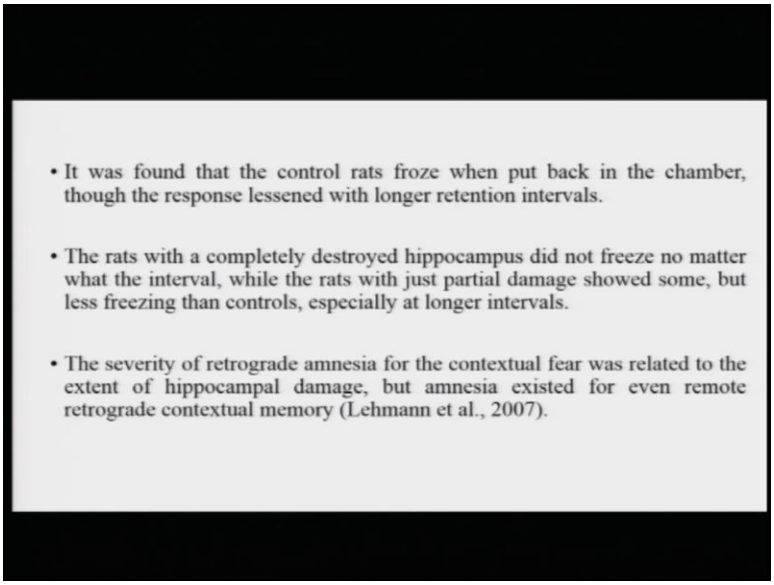

It was found that the control rats who had not gone into surgery froze when put back into the chamber though the response had lessened with longer retention intervals. So, after 2 weeks, 6 months, 1 month as the time increased the freezing response sort of reduced but they did freeze when they were put into that same chamber.

However, rats with the completely destroyed hippocampus did not freeze no matter whatever the interval, not at 2 weeks, not at 1 month, not at 6 months, while the rats with just partial damage showed some, but less freezing than controls, especially at longer intervals. So, there is some kind of retention there but not really as complete retention as was found in these control rats.

Now, the severity of this retrograde amnesia for contextual fear was related to the extent of hippocampal damage, but amnesia existed for even for remote retrograde contextual memories. So, even at 6 months of distance, the degree was there. So, what does this tell us? It tells us that the hippocampus is sort of involved in this kind of retention or in this kind of retrieval of context based memory.

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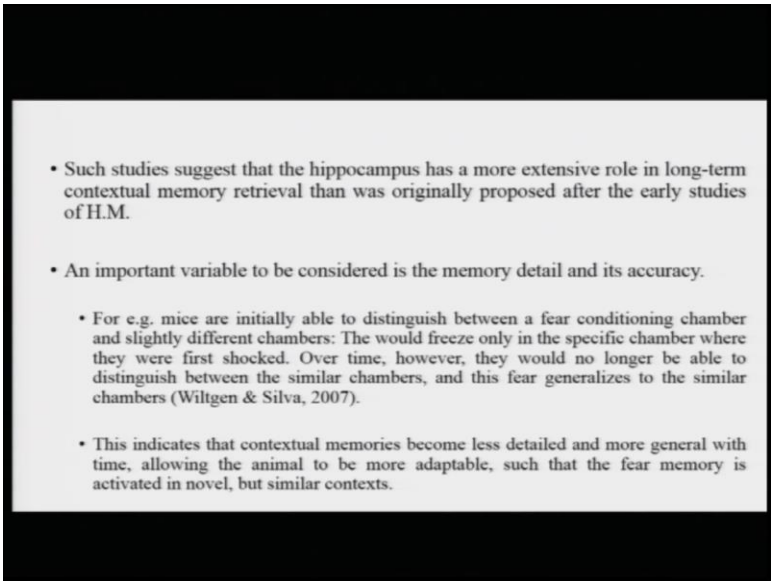

Now, if you look at these kind of studies, these studies suggest that the hippocampus actually has a more extensive role in basically long-term contextual memory retrieval than was originally proposed or supposed after the early investigations with H.M. A very important variable that you need to consider is the detail of memory that is recollected and its accuracy.

For example, it is observed that mice are initially be able to distinguish between a fear conditioning chamber and slightly different chambers. For example what will happen is they would freeze only in that very specific chamber. Let us say, that very specific painting that they were first shocked. Over time however they generalize this.

Over time they will not be able to distinguish between similar chambers. If suppose the chamber is visually similar but it has a slightly different painting then the rat would you know freeze on going into that chamber as well. So, they sort of generalizes. The learning sort of generalizes. What does this tell us?

This tells us the contextual memories become less and less detailed and more and more general when time passes. What it does is it allows the animal to be more adaptable such that the fear memory is activated in novel but similar context. So, generalization has its own advantages and we have talked about that in a separate course in some detail but it sort of tells us that there is a degree of generalization that happens in these animals.

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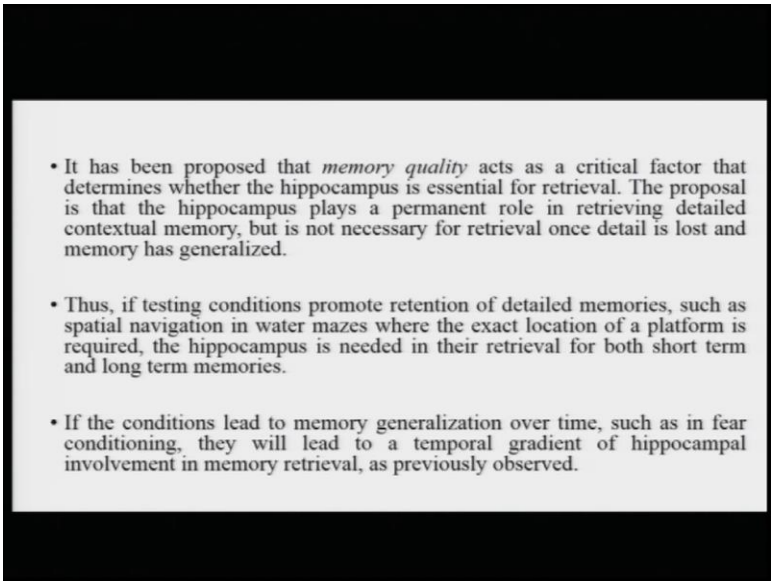

So, it has been proposed that memory quality can act as a very critical factor that determines whether the hippocampus is essential for retrieval or not. So, the quality of memory can indicate whether the hippocampus was really required for it's retrieval or not. So that is the point. Now, the proposal is that the hippocampus plays a permanent role in retrieving detailed contextual memory but it is not really necessary when retrieval is being done for slightly generic memories and not very detailed memories.

So, if the testing conditions promote retention of detailed memories such as spatial navigation in water mazes like the Morris water maze task where the exact location of a platform was supposed to be required, then the hippocampus will be needed for the exact retrieval for in terms of both short and long term memories. If however the conditions have led to generalization of memory over time, such as in fear conditioning like we were just saying then they will lead to a bit of a temporal gradient of hippocampal involvement in memory retrieval as was previously observed.

So, when more time has passed and more generic memories need to be revealed you will see that the hippocampus is less involved. However when less time has passed and more specific detail of the memory is needed then you will see that there is adequate hippocampal involvement in retrieving these long term memories.

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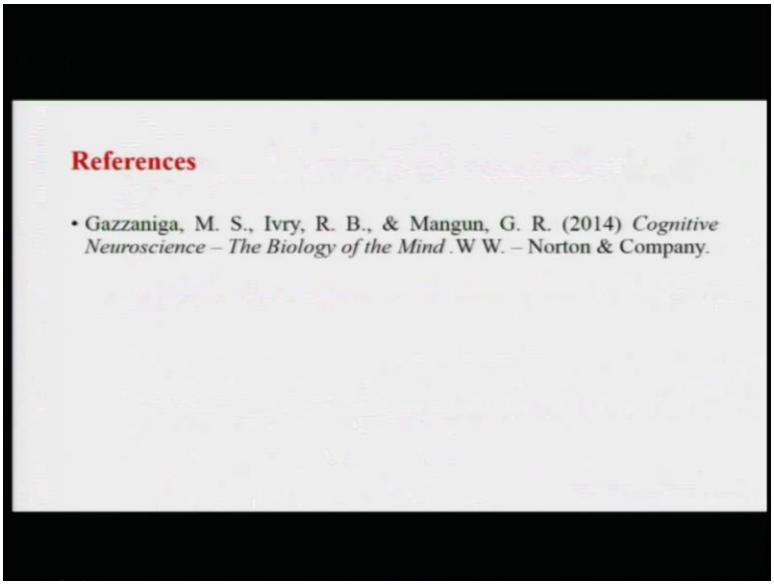

So, I think that is all that I wanted to talk to you about mechanisms of medial temporal lobe memory system today. I will talk about some more topics in memory in the next two lectures. Thank you.