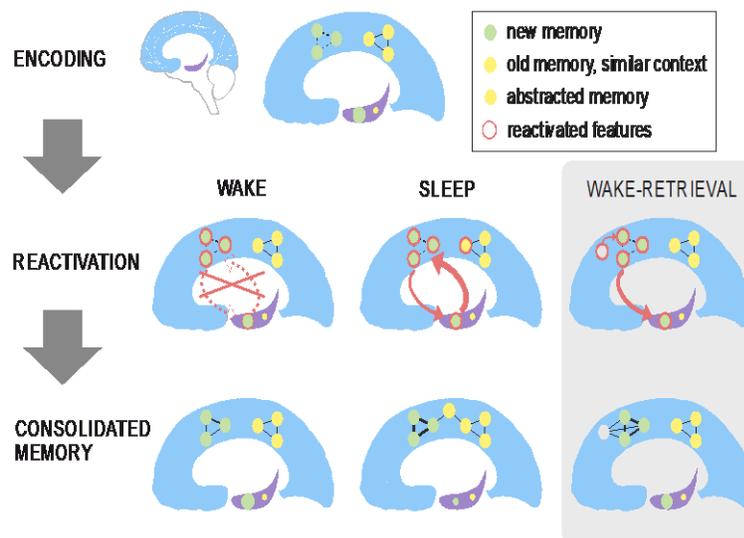


**Memory**  
**Prof. Manish Kumar Asthana**  
**Department of Psychology**  
**Indian Institute of Technology Roorkee**

**Lecture - 40**  
**Memory Reconsolidation - II**

Hello, I welcome you all in the last lecture of this lecture series of memory. As we discussed earlier about the memory reconsolidation, the memory which is in inactive state leads towards the active state upon retrieval and how the modification can be made or done so that the maintenance and modification of the memory can be done. Further down the line, we also discussed about the boundary conditions of memory, the conditions which are necessary for memory to undergo reconsolidation. With this, we discussed about several other aspects related to reconsolidation and consolidation of memory and its relevance.

Today, I just want to give you an overview and holistic approach about the reconsolidation studies which has been done today and also the ideas which people still believe would be very crucial to investigate further down the line about the reconsolidation and revisiting the processes of memory that is the trace consolidation and what other aspects are important in that direction. Let me begin with you about the memory consolidation. How this consolidation process is happening and what do we understand with the sleep literature as I discussed earlier also.



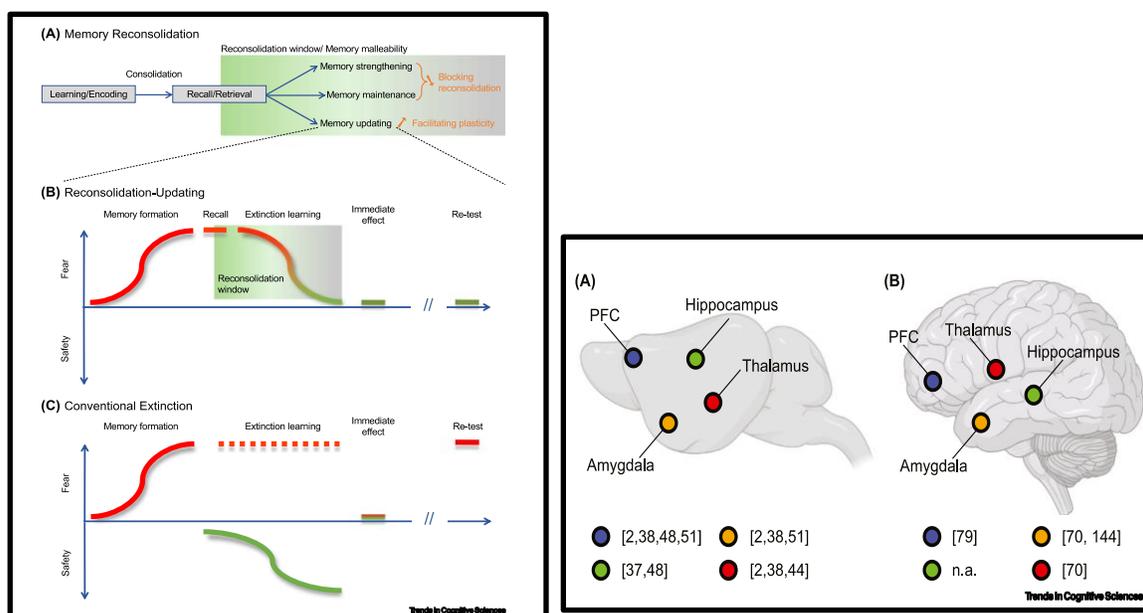
In the sleep literature, when we are doing the and understanding the consolidation process, the sleep versus wake state. So how the trace, the new trace of memory is forming and how this new trace of memory in coordination with neocortex and hippocampus result into the consolidation process. So what we see here is that the encoding state is there and then the reactivation is happening and consolidated memory. Now this encoding state is the acquisition state which we have been discussing several times and this consolidated memory is resulting towards the storage state. And if you all remember the memory process is of three stage process, encoding, storage, and retrieval

So here we are trying to understand how the information is getting stored so then this new cortex which is the developed after the evolution as you can see with the blue color and then the memory structure this pupil which is hippocampus both plays a major role in the formation of new information What happens generally during this reach state when you are collecting the information here, the green dots, when you are forming a new memory, the green dots here in the neocortex area and the green dot here in the hippocampus both collectively together are there which are syncing and storing the information temporarily. So the network is not there as you can see with the cross sign.

The network has still not been established. But what happens when a person goes into a sleep state? This interchange of information begins. And this interchange doesn't happen instantly or out of blue. It happens with a unique milieu of the triple nested area.

What is this triple nested area? Where the slow oscillation starts to generate in the hippocampus and in the frontal cortex. And this gets connected with the spindles and then a ripple starts to occur. This tries to send information from the neocortex to the hippocampus. And this flow, this flow starts to consolidate the information.

And then, when a person is in a very retrieval state, mosaic consolidation has occurred. Then it seems that the networking—the projection from neocortex through hippocampus—is being established. Now, once this reactivation stage is over, the information appears to be stored in the memory system. We even know from the animal literature that when this consolidation, when this interchange is happening, There is a burst of neuroadrenergic activity happening. This neuroadrenergic activity ensures the synchronized reactivation between the frontal cortex (the neocortex) and the hippocampus area.



Source: Silva & Gräff (2023)

So this hippocampal and neocortical memory activation is not happening out of the blue. There is no hemorrhagic activity, and this activity then facilitates the oscillation, spindle, and ripple. As a result, the connectivity starts to happen. And this synchronized reactivation during sleep produces a stronger stabilization of the new memory. As you can see here, once this stabilization has occurred, you can see they consolidate.

Now, the consolidation—as you can see—the green dot in the wake state and in the sleep state. But in the wake state, you can see the black lines are not so solid in nature, which means the synchronization is there, but it is not very robust or strong. While here, if you see, the dark dense line indicates that stronger stabilization has happened during sleep. And that is why it has been recommended that when we learn something, it is important for a person to undergo the sleep stage for memory to be stored and consolidated for a long period of time. So once this consolidation becomes serial, it establishes the network during sleep with other information, with other similar types of information.

It doesn't have to be identical. and neither it has to be distinct. It has to be similar in nature. So, if you all remember, we have been discussing about the categorization and organization of incoming sensory information. So here the categorization and integration of information needs to be similar in nature.

Once the retrieval happens, once the information gets old, then all these information are separate again. But the networking are more stronger and robust in nature. So, for this

stronger stabilization, sleep is important and for the sleep, during the sleep, what activity is happening is actually the worst activity known as neurologic is happening which is eventually resulting into the more oscillations, spindle and ripples and this slow wave oscillation and slow wave spindles which is generated, is actually triggering the activity in the neocortical and hippocampal area which is essential for the memory consolidation.

Now, when we are talking with respect to memory consolidation, earlier we have discussed that what is happening and what reconsolidation is doing. So, when we are encoding and learning and this learning and encoding is consolidated And upon consolidation or upon storage, now we have to retrieve it. Now we have to recall it. So when we are doing this recall or retrieval, what is happening?

Memory strengthening is happening. Memory is becoming malleable in nature. Memory is becoming sensitive. Memory at this stage can be disrupted or distorted easily by any foreign agent. So here the memory strengthening is happening.

Memory maintenance is happening and these two stages of memory strengthening and memory maintenance is blocking the reconsolidation. Memory update is facilitating the plasticity. Why? Because new networking and new connections are required. That is why it is promoting facilitation.

Now this reconsolidation window which we are talking about here How is it happening? So, what you see here on your screen is a conditioning model. This is a fear conditioning model, which is a very standard procedure. This fear conditioning model, what we see, memory formation is happening, learning and consolidation.

Once this is done, then the recall or retrieval is here. And after the recall and retrieval, we enter the phase of the reconsolidation window, which is this window. You can see. During this window, because memory is malleable in nature, mobile in nature, we can update it with some new information, novel information. Or we can treat the memory with any sort of amnesic agent.

So, extinction learning is there. And then, soon after that, We check the immediate effect. What is happening? And what we see is that the extinction seems to be better.

There is no threat at all. People are not having any fear. When we treated the memory during the reconsolidation window. Now, this window we have discussed earlier. It moves from 6 minutes to 6 hours.

Some studies will say 10 minutes. So this is from 10 minutes to 6 hours, up to 6 hours. After retrieval or recall. And then we do the retest. Now, retest: some studies have done it on day 3, 3 consecutive days.

Some studies have done it on day 15. And some studies have done it even after 365 days. And they showed that yes, If you perform, if you treat the memory during the reconsolidation window, you can dampen it or lower it. Now, the conventional extinction—because you have to compare it with the extinction—so what we do is a similar procedure: memory formation is there, but there is no retrieval or recall.

Extinction memory is performed; very nice, beautiful curve shows the decrease in fear. And immediately when you test it, there is no fear at all. However, when you do the testing, we see that the fear returns here. Fear is returning. And this fear return is nothing but a fear relapse, which we also discussed earlier and are going to see today.

Now, if we see this model, we observe that there is a beneficial effect of memory deconsolidation. If you perform, if you treat the memory during this window period. Here you can see two different brains. This is the human brain, and this is the rodent brain. This PFC and this PFC are pretty much the same, and they are doing exactly the same thing.

And then we are also trying to observe the hippocampus behaving the same way. So, the PFC is handling the fear extinction. And this amygdala is targeting the fear memory in both regions. The additional brain structures which are crucial in both studies are the hippocampus and thalamus, the emotional center and memory structures. And what we have seen is that translational studies have shown that the brain structures here are contributing equally.

So, memory reconsolidation is a natural process in learning and memory across organisms. Though in some organisms we haven't observed it, in most cases we have seen that it is happening. Now, in the rodent case, we use this model, and the Pavlovian conditioning model seems to demonstrate easily how consolidation and reconsolidation happen. So, numerous studies have used the Pavlovian conditioning model.

Now, the Pavlovian conditioning model is almost a century old. For more than 100 years, we have been using this model to understand how learning happens and how extinction occurs. And from this model alone, we have understood that after successful extinction,

there is still a relapse of fear. And this fear of relapse, if you see, has three stages in the conditioning model.

One is the associative learning stage, where you are learning it. And then we are doing the safety learning, which is the extinction. And one is undergoing the safety memory. This is the safety memory state. And this is the fear learning state.

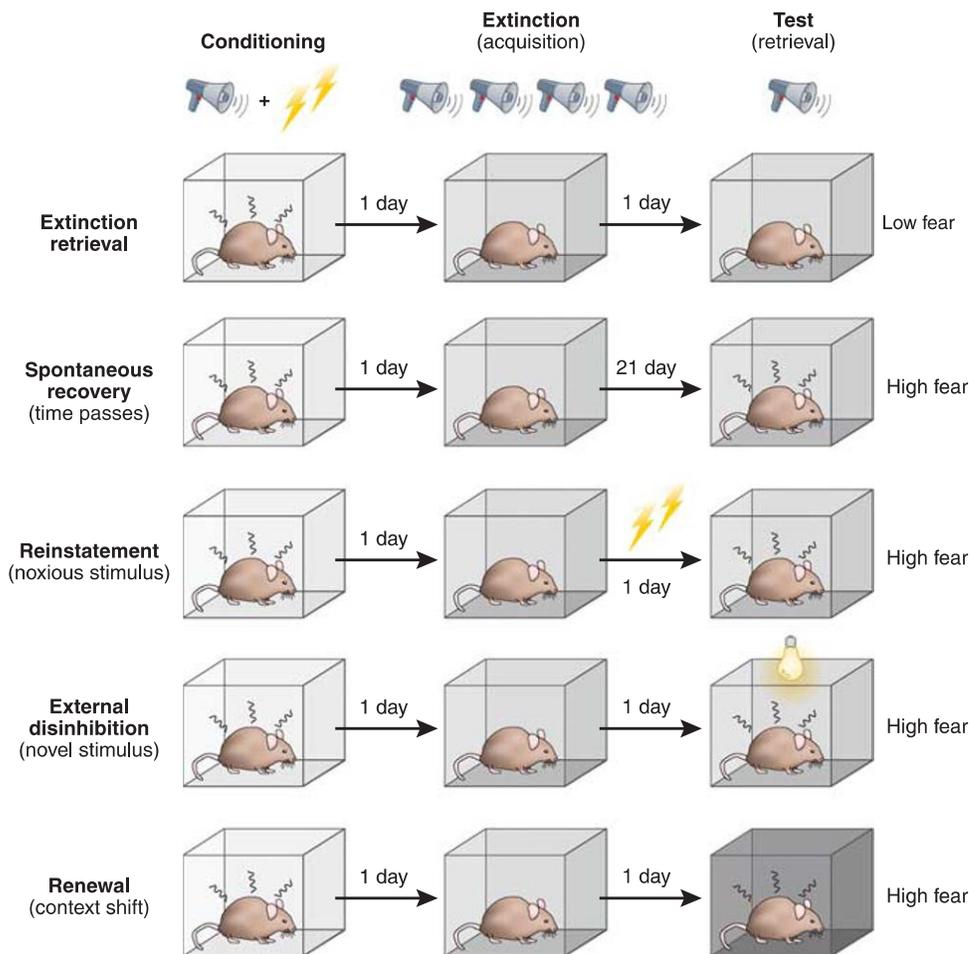
Where the animal is learning with the sound and shock. So every time the sound is given, a shock is also given. And the animal learns that the sound is threatening in nature. And then, during the safety memory, a sound is given. The first sound comes.

Animal shows a freezing behavior, which is a threat response. Then another sound is presented. Animal again shows a threat response that a shock might come. But as the sound appears in absence of the shock, it becomes safety memory. And then we do the testing, retrieval.

A sound is presented. Now, during the extrinsic retrieval stage, we see that the animal is not showing freezing behavior. But when the time has passed, the spontaneous recovery, high fear is shown. Like, after one day you are doing it, no fear. But after 21 days, high fear is there.

Exactly this is what happens in the case with the individuals who are suffering with the emotional or pathological memory. After the successful treatment, they go home and after some period of time, their fear comes back. Now, this retrieval of fear after a sufficient amount of time has passed, we refer it as a spontaneous recovery. Then the reinstatement state. Reinstatement state says that the unconditioned stimulus or the aversive sound or noxious stimulus like in the case here, the sound and shock was being heard.

A shock is presented and it shows a high fear. This is the reinstatement. Fear is being reinstated. And then the external disinhibition is there. External disinhibition suggests that new stimulus is being presented and this new stimulus again brings back the fear because of the mobility. The animal thinks, the human thinks that now new stimulus is being presented which is replacing the previous threat stimuli. So, and the final thing is the context itself, a renewal. When the sound, when the animal is being, sorry, context is related to the space, the space where animal has learned about the fear. So when the animal is brought back to the cage where the learning has happened, it shows again the high fear.



[Source:](#) Maren & Holmes (2016); Kindt and Elsey (2023)

Though fear conditioning model is an excellent experimental model to study anxiety and related disorders, However, insight into complexities of fear and phobias are still unclear. We have been studying this model last several years but still till date it hasn't been provided lot of insight related to fear and phobias. What is the nature of phobia? How can we overcome this?

How one could make this extinction memory or the safety memory more robust in such paradigm? And how these transference is happening, how the safety transference is happening, such insights we are still lacking, though the model is very effective and efficient. And not to mention here, we have been discussing this, that conditioning model is something which people have used to demonstrate the reconsolidation under many

instances. Now one more aspect is there which where people with respect to reconsolidation and extinction they are addressing is that is extinction same as memory reconsolidation or is reconsolidation is same as extinction.

Now it is very important for us to understand that extinction, memory extinction and memory reconsolidation are two distinct paradigms. For extinction, there is no reactivation is required. For extinction, memory doesn't have to undergo malleable nature. For extinction, the exposure of the safety memory is required. In this case, in the animal study, the exposure of 30 minutes of context is enough.

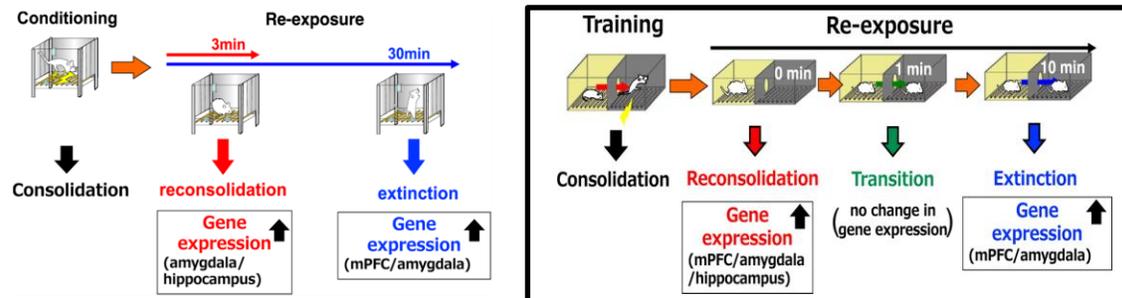
If animal is brought into the context for less than 3 minutes or equal to 3 minutes, then that presence is reactivating or acting as a retrieval or recall of the fear. So when the animal is brought back to the cage where the animal has learned about the fear, within 3 minutes the animal learn about the, collect the information from his brain that now this is a threatening environment. And if animal stays here in the same environment for 30 minutes, then he starts to build safety memory. So this exposure, re-exposure, sorry, because here already the exposure has happened. So the re-exposure of the environment with respect to time is

clearly indicating that in one case memory is getting reactivated and becoming malleable and if you are not doing anything then it is going to start with the same impression and this is what extinction is happening now they do not share any mechanism theory consolidation is a distinct process and mechanism, then the memory extinction. Even what you see here, once the consolidation has happened, light and dark space, whenever the animal is coming into the dark space, he is getting a shock. So animal has, rodents do not like to be in a bright area. They always look for a dark area.

So when you are forcefully making them learn not to be in a dark area, they learn and they try to stay in the light area. Now when they are in the light area and you are bringing the animal back into that same environment, then animal will undergo reconsolidation. If you don't do anything, if the shock is not given to them, then animal slowly moves from light area to dark area because it prefers the dark area. During this transition, no protein change is happening. No protein expression is happening.

But once the animal stays here more than 10 minutes, then the new protein expression starts to happen. And this protein expression is happening in the media prefrontal cortex or amygdala. So the diagram which I showed you earlier about the rodent brain and the human brain, exactly this is what is happening. During the extinction learning, new

protein expressions, new genetic expressions are being expressed into the brain. So here, on one side, when we are talking about the time-dependent processes, on one side, we are talking about the protein synthesis dependent.



[Source:](#) Kida (2023)

And more than that, what is crucial here is these 10 minutes. That before 10 minutes, Expression is not happening. So it requires roughly, approximately 10 minutes of time for our brain to transition into a similar inactive state—sorry, active state—as we discussed earlier. An active state where memory is malleable, labile, and sensitive to disruption.

So from inactive to active state, it takes at least 10 minutes, and once it becomes active again, you can treat the memory again, and then it will move back to the inactive state—reconsolidation. The necessary conditions for memory reconsolidation—we studied that memory reconsolidation occurs in organisms across species. Crabs, fish, snails, honeybees, humans, and many more examples are there. So what we understand is that reconsolidation is a fundamental process in learning and memory. It is happening in all these species.

However, we also have documented that some field applications exist. These field applications indicate and I notice that not every time does memory undergo reconsolidation, and if memory is not undergoing reconsolidation every time, then there must be some controlled parameters. And these controlled parameters we tried to address with boundary conditions of memory—that there are boundary conditions of memory. So this failed application could be happening because of the boundary condition—that is, the age of the memory, the strength of the memory, or the novelty being brought into the memory reactivation.

So if you add the novel element during the memory reactivation, the chances are there that it will undergo into reconsolidation. But if novelty is not there, then it may not. We even understood that altering the temporal association between CS-UCS Which means that at the time of acquisition, the CS-UCS bonding is very strong. If you increase the CS-UCS duration, as we saw earlier in the previous diagram here, that the context, if it is the CS and the shock is not given to the animal for next 30 minutes, then it will start acting as a safety learning.

So, varying the temporal association between CS UCS could also result into that. So, when the CS and UCS was being followed by 2 seconds, if you increase the CS UCS to 4 seconds to 4 minute, you will see alteration of these association temporal can also affect the reconsolidation. We even understood that the strong memories may be prone to change, may not be prone to change, may not be disrupted, cannot be impaired upon reactivation. But we know with some empirical evidences have suggested that the strong memories can also undergo reconsolidation but it might take a little longer retrieval trial. It might take little more retrieval trial or recall than the normal memories.

However, some researchers believe that the boundary conditions do not exist at all, which we discussed earlier. Because all these boundary conditions of memory, we have been trying to discuss with respect to the conditioning model. CS-UCS association, reinforcement level, prediction error, UCS nature, CS nature, context. And if these things are not there, memory cannot undergo reconsolidation. So, some researchers believe that there is no such thing as boundary conditions of memory.

Memory itself is very complex in nature. It does not require those; it does not depend on learning, training, or age parameters. It is an important aspect for us to understand the clinical signs and how memory reconsolidation is connected. We know that reconsolidation is a mechanism of change where modification can happen, where updates occur, and where maintenance takes place.

So, the activated memory upon reactivation may be targeted with drug administration, and if this happens, then we are modifying the memory. So, once the memory is in the reconsolidation stage, once there is a reconsolidation window—which is from 10 minutes to 6 hours—we administer the network, let the mechanism of change happen, and a new memory with updates will be stored. This is how we can treat pathological memory. But for the memory to undergo reconsolidation, prediction error is important.

In prediction error, what we must understand is that when the subject expects an outcome, but the outcome is different, when the participant anticipates an outcome, but the appearance of the outcome is different, there is an error. A prediction error occurs.

So when the animal or human is learning at the time of fear learning, CS, UCS, sparing, doing fear learning, then at the time of safety memory, they are even expecting CS, UCS to appear. However, this does not come because there is CS, but no UCS is present. So, people are expecting this CS-UCS occurrence, but in reality, they are having only CS presentation. The larger this prediction error is, PE, if you refer to it as such, the memory will become labile in nature. Labilization is going to happen.

Memory will become malleable in nature. The higher the prediction error is, the higher the memory malleability will be. But the question arises here: does prediction error occur under normal circumstances in a controlled environment? But with a clear sample, is it going to happen or not? There is a critical condition to trigger memory reconsolidation.

Failure of replication of memory reconsolidation has indicated that not all memories undergo reconsolidation. This becomes more critical in the case of clinical samples. Clinical samples include subjects suffering from post-traumatic stress disorder, subjects having phobia, and subjects having anxiety. So memory reactivation also depends upon individual differences. Many studies have shown, and even we have shown, that in the case of genetic polymorphism studies,

Different adults, individuals have different responses towards a threat. Some adults are more prone to developing fear than others. And if they are more prone to developing fear, then for these individuals, it is very difficult for the memory to undergo reconsolidation. The important aspect, as a researcher, is to understand the optimal conditions for memory reconsolidation. Particularly in clinical science.

Which is very, very limited. We do not know what the optimal conditions for memory reconsolidation are. Under those conditions, if we understand when memory is undergoing reconsolidation, that information will be highly relevant in clinical science. But we cannot ignore the fact that the last two decades of reconsolidation studies have had a great impact on human memory research. And to date,

Researchers are still investigating the concept of memory reconsolidation and trying to translate this into different memory studies and also with different organisms. Let us spend a few minutes here to understand memory reconsolidation and the different

techniques we have used. We have used neural stimulation techniques like transcranial direct current stimulation and transcranial magnetic stimulation. To target memory reconsolidation. Once the memory becomes labile, once the memory moves from an active to an inactive state, we treat the active memory with neural stimulation.

Studies have shown the potential that a drug-free paradigm using neural stimulation can be offered. The drug administration, particularly prazosin, seems to be very effective in the blockage of pathological memory, even with a clinical sample. Translation research is required. Not a lot of translational research is present which indicates that memory reconsolidation is a fundamental process in learning and memory. Behavioral methods such as flooding or exposure therapy during the memory reconsolidation window seem to have a significant effect which Schiller in 2010 demonstrated.

Some studies have shown the cognitive behavioral therapy during memory reconsolidation. If CBT is applied or implemented during this reconsolidation window, it can modify the memory. And its effect is more robust than only if CBT is applied. Some studies have shown the genetic polymorphism, such as we published a study in 2015. BDNF, brain-derived neurotrophic factor,

which is highly expressed in the hippocampus, seems to have a role in memory reconsolidation. We even showed from our group about the effect of music. When the music is applied during the memory reconsolidation window, it can modify the memory and can provide a novel methodology towards a drug-free paradigm in anxiety and related disorders. Some studies, some animal models have used optogenetics to understand how the process is entirely happening and few recent literatures have even entered into the arena of virtual reality and to see how memory reconsolidation idea, process could be implemented in virtual reality to offer a more robust, drug-free paradigm.

Let me give you an overview of what we studied in this entire memory lecture series. In this entire lecture memory series, we started with the philosophical perspective of human memory. Then we went on to understand the neuropsychology of memory. What are the different distinct brain regions that come together and help an individual to encode, store, and retrieve. How are we retrieving the information?

How are we retrieving and recalling the information? Types of retrieval. We even understood the classical information processing model or classical memory processes.

Sensory memory, short-term memory, long-term memory. And how Baddeley and Hitch suggested replacing short-term memory with working memory.

And what is the reason behind such a replacement? We even further down the line studied long-term memory, and in long-term memory, we understood declarative memory, where we studied episodic and semantic memory. Further, we studied how we forget information. We started with the classical experiment of Ebbinghaus's memory drum experiment and studied the learning curve. How this memory forgetting moved towards memory disorder.

We studied different types of memory disorders. And finally, we concluded our lecture series on reconsolidation. The new topic, the recent topic, the highly investigated topic in memory literature is how memory can be modified. So, what did we study? In this lecture, the final lecture of our memory series, we discussed how memory consolidation happens, sleep versus wake states, how memory consolidation takes place, memory reconsolidation, and extinction.

We also covered the necessary conditions for memory reconsolidation, what clinical science says about memory reconsolidation, and which important aspects in clinical science are relevant for us. We discussed memory reconsolidation and different techniques researchers have used to date. Then, I gave you an overview of what we studied in this memory lecture series. For further studies, I recommend this book on memory reconsolidation by Christina and Albany. This is a very nice and decent book. If you get time, spend some time with this book. You will gain a lot of understanding about not only memory consolidation but also memory reconsolidation processes.

With this, I rest my case and conclude this lecture series. Thank you all for being here with me for the last 8 weeks and learning together with me about memory and its processes. Thank you.