Module:
Biological Foundations of Mental Health

Week 4
Biological basis of learning, memory & cognition

Topic 1
Learning, memory and synaptic plasticity – Part 3 of 4

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Lecture transcript

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Welcome to Part Three of our lecture series on synaptic plasticity and learning and memory. In this part, we will discuss hippocampal memory tasks. That is because we need to understand behavioural tasks, before we can explore the question of a long term potentiation is an important learning, memory mechanism.

As you know, the hippocampus is very important for learning memory in humans. That is thought because surgical ablation of the hippocampus affects memory in patients-- patients that have been treated for epilepsy, and unfortunately then suffering severe memory impairment. However, such studies lack a little bit of precision because when you do surgical removal of a brain area, you would affect a number of different brain areas and not only the hippocampus.

So, one would need to do animal experiments to know exactly, kind of like, what the role of the hippocampus is by just lesioning the hippocampus, for example. So the behavioural task we're going to discuss now are all sensitive to lesions of hippocampus in rodents. And we will primarily focus on mice because mouse studies have been used primarily to address the issue of long term potentiation and memory. But it applies also to rats.

Before we go into the task, we will distinguish between different memory processes. And then we will go into behavioural tasks.

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Memory can be distinguished also on the time scale and by the brain areas involved. So we can talk about a short term memory, or long term memory, a working memory, which is very short lasting. And then the brain areas involved, so memories that require the hippocampus, memories which do not require campus, for example memories that require the cerebellum. And so the focus here will be really on, as I said, on memories that require the hippocampus.

So if you were to lesion the hippocampus, the memory is impaired. But it's not to say that memory is stored only in the hippocampus. It was probably stored also outside the hippocampus. But the hippocampus is just an essential component of memory. Then basically, we will focus primarily on long term memory, because long term potentiation is thought to be an important mechanism to store memory for very long periods of time.

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In humans the hippocampus is important for declarative memories, as I mentioned in part one briefly. So it's important for knowing who the prime minister is, or who a particular sports star is, or other memories, kind of like for example, when you remember where the cinema is. These type of memories you are aware of require hippocampus.

Of course, in rodents we cannot really speak of so-called declarative memories because we do not know what rodents are aware of. So, therefore, this definition of declarative memory in rodents doesn't really apply. However, in rodents, it has been shown that the hippocampus is particularly important for spatial memory. So memories of to find a particular location in a space. Or contextual memory-- so these are memories to remember a particular environment.

These types of memories have resulted basically from the discovery of places in the hippocampus. So these are cells that fire only when an animal is in a particular location. So, therefore, being discovered by John O'Keefe at University College London. And their discovery basically suggested that the hippocampus is important for making a spatial map of the environment. And in humans maybe even a cognitive map, maybe in animals also cognitive map.

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To study spatial memory, people use the so-called water maze. It's a task that was developed by Richard Morris at St. Andrews at the time. So what Richard Morris did is he basically designed a swimming pool that contains a submerged platform. And the water in the swimming pool is made opaque, milky. We use in the laboratory white nontoxic paint for children. So the animals cannot look through the water and cannot see the platform.

What the animal has here is basically a platform it can rest on, as you can see on the right side. And then a swimming pool, basically the animal cannot climb out. So what the animal can learn in this task, ultimately, is to locate a platform location. Using these cues in a room, like for example, this chair or this picture on the wall, so they can basically learn how the map of a room looks like, and where in that map a platform is located.

Now this behaviour task is really complicated. So the animal cannot learn this in one trial. So it's a very difficult task. What the animal learns here is many different things. So when you put for first time a mouse into the water maze, the animal will try to climb out of the pool. So they swim around the rim of the pool to try to get out until it has learned that there's no escape.

When the animal goes into the next learning phase, it will explore the environment. So in another trial, it will basically swim around randomly, until it finally bumps accidentally into a platform they can rest on. So the animal will learn that there is actually a platform I can rest on. So it learns to use the platform, so by swimming around randomly.

When the animal gets more clever, and it will finally develop a strategy to locate the platform. So for example, it might learn that the platform is located to a particular distance to the pool wall. So then it can swim with a particular radius to locate a platform. So these are kinds of strategies that are so-called procedure, basically. They're relatively efficient, but they are not ultimate spatial learning.

So these procedure strategies ultimately lead to spatial learning. Every animal learns that a platform is located in a particular location in the room. And once it knows where in the room it is, it uses the map, the spatial map, to navigate to it, the platform.

Now we can test for spatial learning by after training, in that we remove a platform from the swimming pool and allow the animal to search for the missing platform. So if the animal then swims toward the missing platform location, and spends most of that time doing the so-called memory probe trial when the animal has remembered the spatial location. So the animal searches in the area where the platform used to be. Contrary, the animal searches an equal amount of time in all areas of

the swimming pool, when the animal indicates a random search for a missing platform in the memory probe trial which shows what the animal has not learned the spatial location.

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So this is what one does in the water maze. And now I'll show you an example. So this example is of some work which we have done in the laboratory. What we see here is after different training sessions. We had 15 training sessions. We trained four different types of mice. So kind of like, for simplicity, let's just focus on WT, so wild-type mice. So these are the open symbols. And what we record here is the latency in seconds. So this means the time the animal needs to reach the platform.

So for example, training session one indicates that wild-type mice, the open symbols need between 60 and 70 seconds in average to reach the hidden platform. Well, already in training session two, this latency has declined to 30 seconds or 50 seconds. And with more training sessions, basically the latency decreases until finally the animal reaches some kind of asymptote. So within 10 or 20 seconds it can reach the hidden platform. So the animals have improved over time with a learning curve. And so it's clear learning in these wild-type animals, normal mice.

In contrast, the black symbols indicate a mutant mouse. We discuss this mutant mouse later in more detail. But this mutant mouse, basically, has not improved over time, indicating that the mutants do not learn. So something is impaired in these mutants that prevents learning. As I pointed out earlier, such a curve, such a training curve alone, is actually not sufficiently indicative of impaired spatial learning in the mutants or of spatial learning in the wild-type mice.

That is because wild-type mice could use, for example, an alternative strategy to locate the platform. So we could circle the particular radius for example. And the mutants may have some kind of like performance abnormalities. But let's not go into mutants now. Let's just focus more on how a normal animal, a wild-type animal, would learn. And so, basically, just looking at this training curve alone, is not sufficient evidence that there's spatial learning in the wild-type animals.

To get the evidence, what we have to do is we have to give a memory probe trial. This indicates the different strategies again, just making the point that there's some learning, that there's no escape. It's a first phase. And the use of a platform, basically one strategy learning, so these three things can happen when you get an improvement in wild-type animals. But to the animals use really is spatial strategy.

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For a spatial strategy, we do a spatial memory probe trial which is indicated in this slide here. So if we just look at control animals without normal animals, you can basically now analyse the search patterns. So the platform has been removed. The animal is allowed to search for the missing platform. And we divide the pool into four quadrants. The quadrant of a platform used to be the training quadrant and and three other quadrants.

And you can see from this control example, that most of the search time the animal spends in the training quadrant, that's also been quantified below. You see that the animal spends about 60% of the search time in that quadrant and not much time in the remaining three quadrants, indicating that the animal has a clear spatial bias. So it clearly remembers where the platform used to be. So there's evidence for spatial memory. So spatial learning has occurred.

On the right, this is a drug-treated animal. We'll come back to this in a moment. Just to make the point, this would be an animal that does not have a spatial memory because this animal searches now equally in all four quadrants, as quantified below. You can see that basically the search time in the quadrants is between 20% and 30%. For each quadrant, there's no difference between the quadrants indicating a random search. So there is no spatial memory in these animals.

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Now a more simple task that has been devised to assess for hippocampus dependent learning, is the so-called passive avoidance task. So this is a task that can be learned in a single training trial. So what's done here is a rodent is placed into a lit compartment and the lit compartment is connected to dark compartment. So a rodent, like a rat or a mouse, likes to be in the dark. So the animal would go into the dark, once it is placed in the lit compartment. It goes almost immediately into the dark, where a door can be closed and a mild foot shock can be provided.

So the animal here learns when that going into the dark could be dangerous because a mild foot shock is provided. So the animal, therefore, would be learning to avoid to go into the dark. So at the time of testing, when the animal is placed back into the lit compartment, the animal avoids to go into the dark. So this is a passive avoidance task because the animal does not have to move to avoid the dangerous situation. It's passive.

So passive avoidance requires the hippocampus. So if the animals would obtain lesions of the hippocampus, then the animals would not remember. But in the dark there was a shock, so we would go again into the dark compartment. And they would just have no memory of the association between dark and foot shock.

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So a typical example of this task is shown here in this slide. So in panel A, you can see a wild-type animal, so normal wild-type mouse. So at the time of training and the open bar shows you that the latency to go into the dark is below 50 seconds. It's maybe like 20 seconds. But after the training, after one training trial, a wild-type animal avoids to go into the dark. So it now spends more than 250 seconds in the lit compartment.

And on the right, as comparison, it's just a mutant animal. And this mutant animal has also a very short latency at the time of training. So it's motivated to go into the dark, where it gets a shock, but it will not remember that it has received a shock in the dark, basically. So again in this mutant something, some process is impaired that impairs hippocampus dependent memory formation.

So this is the one trial learning task. So this is in contrast to the water maze that requires many training trials. And the advantage of one trial learning tasks is that all the animals learn at the same time, so after one trial that is. So if you want to study molecular or cellular processes that underlie learning and memory, then this is a great task because all the animals are kind of synchronised. They have learned at the same time.

In the water maze in comparison, some animals may learn after training session five, others after training sessions seven, and so on. So the animals are not synchronised. So they learn at different time points. And it's very difficult to find out when each animal has learned. So therefore, there is much more noise in analysing molecular and cellular mechanisms that underlie learning and memory.

The other advantage of one trial learning task would be that one can easily distinguish from short term memory to long term memory. So that is the advantage of the synchronisation. So that because we know exactly when the animals get trained. And then we can look for example, for short term memory 30 minutes after training, as indicated in this cartoon here. It's in panel B. So this is from memory 30 minutes after training. Again the wild-type animal show an avoidance. The mutants do not show an avoidance. So the mutants are impaired in short term memory. And we can look at long term memory, which is usually done 24 hours after training. And we basically see that the long term memory is impaired in the mutants but not in the wild-type animals.

So the mutants have an impairment in short term and long term memory, in this case. But because short term memory is impaired, it's likely that this is because of the long term memory impairment.

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So this part introduced you into some behavioural testing of protocols for assessing hippocampus dependent memory.

We needed to have this session basically to familiarise you with these behavioural tasks because these tasks have been used to study whether LTP is a memory mechanism. So LTP was measured in the hippocampus, these are hippocampus dependent memory tasks. And the questions in the next part will be is what happens when we block the induction of long term potentiation. What happens to learning of memory? What happens if you block the maintenance of long term potentiation, that would erase existing hippocampus dependent memories? And so on.