Learning about Learning A Course on Neurobiology of Learning and Memory
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Lecture – 15
Sign Tracking vs Goal Oriented; Learning Linking complex behaviors to simple molecules – II

Hello and welcome to lecture 15; this would be continuation of lecture 14 where we are trying to differentiate the Sign Trackers versus the Goal Oriented behaviour or goal tracking. And then we are trying to link these complex behaviours to simple molecules. In the lecture 14 we talked about three different behaviours, three different schemes where which you can subject the animal to. And then from there those measures we are the idea is if you can classify them in universally and then say if there is an emerging trend that we can talk about. First remember our, the high responsiveness or lower response I will group we did that, I mean we people more specifically Flagel.

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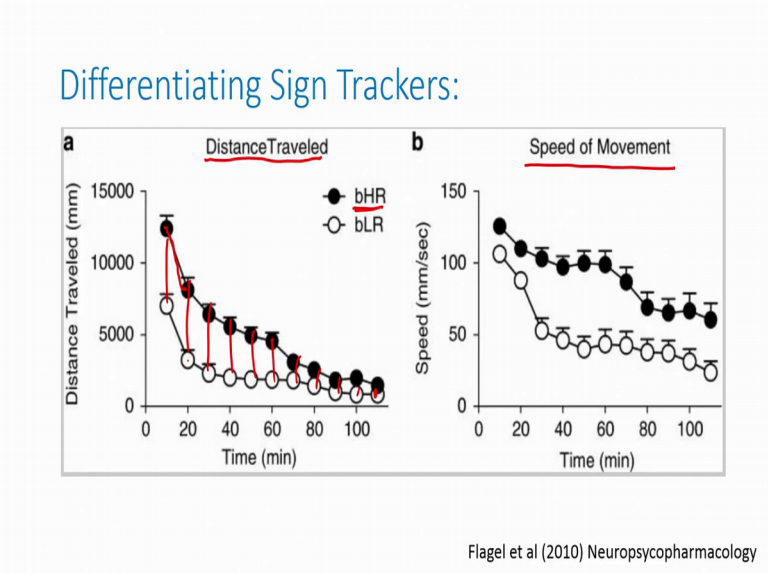

And a Flagel et al group headed by Hood Akil and they at University of Michigan they actually did this experiment wherein they took those animals that they are high low or locomotor active right. And then we talked about breeding them, in breeding them within themselves and then generating a breed of rats that are really high responsive they call it

as high responsive. And the reason why they call it as high responsive is that as you can see in the graphs here they are measuring distance travel.

And speed of movement in this locomotor assessment task where, clearly the high response rats are moving a larger distance clearly as a function of time they have explode enough they are going to come back down so, but that is the notion right. So, they are high responsive, they are exploring a lot and you can actually see those curves that the black circles black filled circles the high response guys are responding at each point higher than the low response group eventually meeting them at as an asymptote not just that all throughout they are also moving at a higher velocity.

So, it is only right to call them as high responsors they are moving fast really, having generated this kind of two breeds; high responsive bread and a low responsive bread; next they wanted to ask they wanted to estimate they wanted to estimate how do they perform when you are actually asking this sign versus the goal direction.

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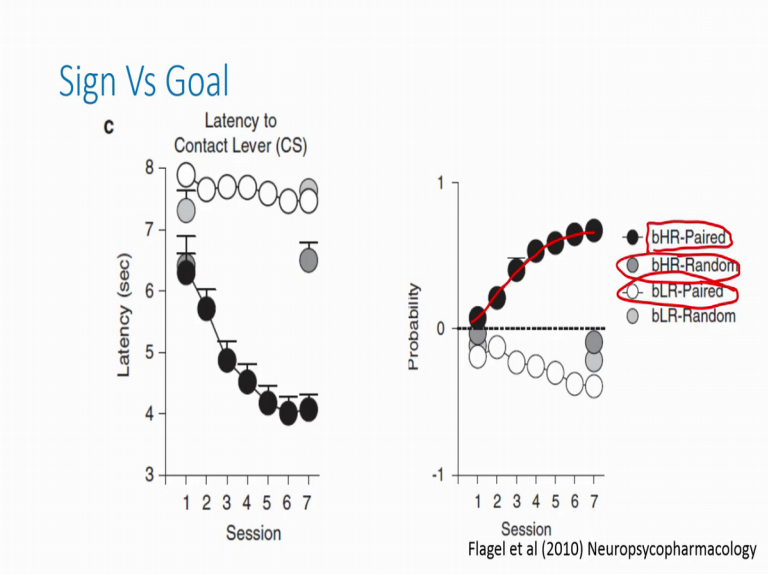

Remember the sign versus the goal or trackers they differ in their approach to the in that skinner box kind of an experiment there they differ in their approach to the lever or the food alright. So, now if you look at the probability that the high responsor would go towards the lever. As a function of the training that is key here you can actually see that the probability constantly keeps going up and it reaches a maximum; I mean this again a beautiful Wagner curve while learning. So, it is a learned response, but they what they

learn is the learn to go to the lever that the where they want to press. On the other hand that is what this HR paired means paired means they are paired with the food outcome.

Clearly you need the pairing because if you do the same group and then do the random pairing right there which is there is no contingency of lever press with the food they are at some chance level around 0. On the other hand this does not have any effect and the low response guys they cannot they are constantly somewhere else they do not go to the lever at all. And that is clearly did its not just they go to the lever, but they also go to the lever in a very very fast time right.

So, you see that the lethargic slow moving guys we call the goal oriented guys towards they take a quite a good amount of time before they actually come to the lever and then say that they are going to press the lever. They do come, but they come in a very slow fashion. On the other hand these signed director sign tracking guys really learn fast and then the latency falls down just the way we looked at the probability of them going to the lever versus the food its going up. This the time that take to go to the lever comes down they not only reach to the lever more often, but they reach faster too ok.

So, clearly HR group are sign tracking while I have not given the evidence here of LR group being goal oriented, but you can actually go into this paper and look at this there is a continuation of this graph. If you actually were to ask latency to reach the food magazine right, the magazine where the food has been delivered this curve should be exactly reversed that you will have open circles, the lower group learning to reach the food place much more faster they will reach faster and so on and so forth. But the bottom line is you can classify them into sign verses goal group based on the moment a high response versus a low response, having done that they wanted to ask how about their behaviour in other tasks.

Such as the impulse control right we talked about the DRL scheduling in the last lecture remember when you this is the task where you actually have to press the lever to get the reward. However, you need to be able to suppress that feeling of pressing the lever the for a certain period of time. If you do not suppress, but you end up pressing before a certain period of time you will not get the reward, despite that how many lever process do does the animal do if it the, if you see that the animal is doing more number of liver

process even in that condition you tend to call them as lacking the impulsive control or they are impulsive to start with. Now, what happens in that task in this group of animals?

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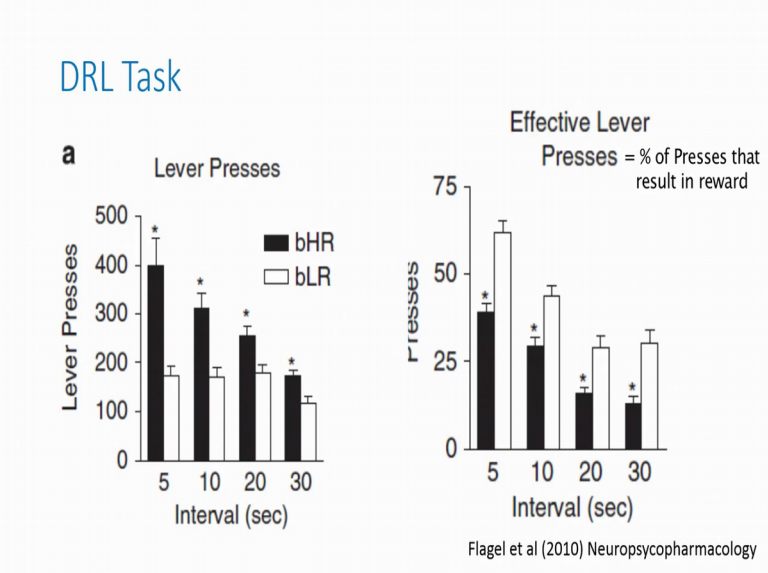

And again the same paper what they show is that for the high response group when you have a lower period requirement right. So, if you have to wait for a shorter period ok, without pressing the lever they do it miserably as against the lower group. So, they you can see that as a function of this different time intervals they do not I mean the low responsive group at I mean there is a constant response where it does not change their responsibility at all; however, this interval has a huge effect on the high response.

When that tau is small they cannot stop they cannot just control the urge to press the lever they tend to press more number of times and of course, when the time gap is large enough they do catch up no doubt about it. But the point is the smaller intervals which is also more driving to press the levers they cannot just control. In fact, that becomes much more clearer if you actually plot this in a slightly different way you plot in you ask how effective were they in liver process right an animal that lacks an impulsive control who you would think that they are less effective ok.

Now, if you do that and clearly you can see that the effectiveness all right effective process are extremely high for the lower low response guys compared to the high responsive. Once in all the intervals, but it is more so, in the shorter intervals. So,

anyway the longer intervals there is not much problem they do have a good estimate its the shorter interval that is hard to control and they miserably fail the HR group.

Now, the point is you have now rat that is a rat breed that is high response we call it as high response group has this very peculiar characters they are high moving they are more explorative, they are lacking to some extent on impulsive control and they are sign directed. So, if it is so unique I mean so, distinct from the other group the low responsive group and we got this segregation of high responsive versus the low responsive purely based on breeding selective breeding right, we picked out those animals that were moving high that where to start with our responding more in loco motor activity.

And then bred them with more of its kind and then generated this bred then we might be looking at a genetic basis are more interestingly they argued that maybe a striking simple molecular basis for this behaviour. What could be such a molecule a molecule that actually drives an animal into completely at a different characteristic different regime of responses in this varying amount of tasks and that separates them into the from the other group this group was looking at different classes of neurotransmitters.

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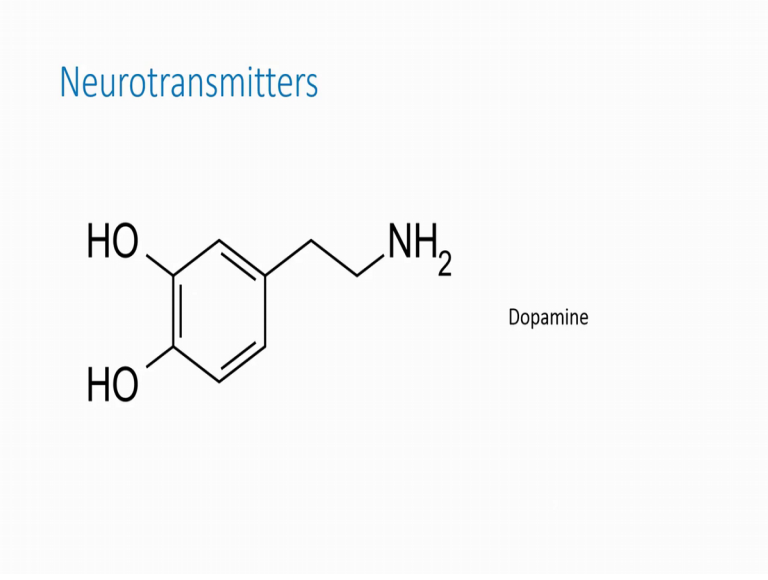

Neurotransmitters are small molecules they help transmit the information from one neuron to the other in brain. And this group was particularly interested in asking the effect of dopamine neurotransmitter a small molecule neurotransmitter in controlling these behaviours. Specifically, they were trying to ask what happens to dopamine in this

group of animals when the animal is learning the task dopamine is known to be a reward signal. So, is it a reward mismatch that is it possible that the high response elements were thinking pressing the lever is the reward I mean that they equating that to be the reward versus the low responsive element are clear unless until they get the food there is no reward.

So, if that is the case here is a very direct testable hypothesis, what you can actually do is that you can look at the dopamine release in these animals as a function of learning how would you do it? You these being a small molecule you need to do some extra you need to take some extra steps to actually be able to measure these molecules in the brain. And not only you want to measure these molecules in the brain you want to measure these molecules and their concentration while the animal is actually engaging in a task.

So, there are ways to do it the way that we are going to look at and the these people have done is using something called as a cyclic voltammetry its essentially using an electrode and looking at the response of this electrode that gets altered because, of the presence of these chemicals right the did mean the different molecules have different propensity to get oxidized and reduced and thereby they have the, they leave their unique signatures. And using these signatures you can measure not only the presence and absence of the molecule, but. In fact, you can do it quantitatively you can actually measure the amount of such molecules in different regions of the brain.

So, they put in these electrodes inside the rat of these two groups and when you whenever you do such kind of a external like surgery and implanting to the electrode one of the main thing that you want to ask is does your phenotype. The phenotype here means the expression of the differential behaviour in these two breeds right the breed we classify them as high responsive element because they have a higher locomotive action they are sign directed and lack impulsive control right do they preserve and the first task is to actually you want to test them and it turns out that you they are preserved even after the surgery. And, more interestingly the point of doing the surgery is to be able to measure the dopamines and when you do that.

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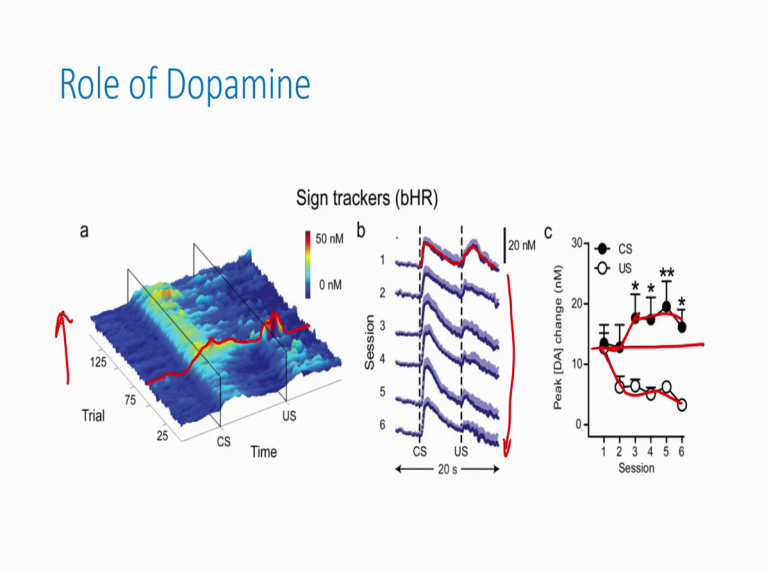

What you are looking at these responses and these responses as a function of time during a trial and as a function of the trials themselves. So, on the left even though it looks like a pretty intense slide I let me walk you through this slide one at a time right. On the left what you are looking at is the response of these animals as a function of different trials right that is across this. So, if I were to look if I want to look at let us say 75th trial I am going to look at this particular line here how is it actually proceeding forward.

On the y axis here or the z I mean y axis here the height here of this different peaks represents the amount of dopamine. So, that is for to make our job easy they have colour coded it. So, if you see a deep red then that would correspond to 50 nano molar and a low black or a blue would correspond to a 0 nano molar of dopamine, superimposed on that are the time points at which the CS and the US is being presented ok.

So, now you can see in the sign trackers you have this classical behaviour which is as a function of different session the amplitude of the dopamine response around the CS and the US changes. It starts with almost pretty high peak of the US dopamine there is a dopamine release following this I mean following the CS as well as the US, but progressively the amount of dopamine that gets released for the US that the second peak goes down in this case right that is the progression of the sessions.

And you can actually measure this peak and plot it as a function of sessions what they have shown is that from the start level if you look at the dopamine response towards the

CS these dopamine response towards the CS goes up in this HR animals high responsive animals while for the US it comes down that is critical here. Now, here is the example where the animal actually tries to think I mean the why the actual animal actually thinks that the CS is the US it is the CS itself is rewarding enough its actually saying that is enough dopamine here right I mean that is to make it think that it is rewarding they are sign trackers right. Now, what happens when we look at the same kind of measurements in goal trackers.

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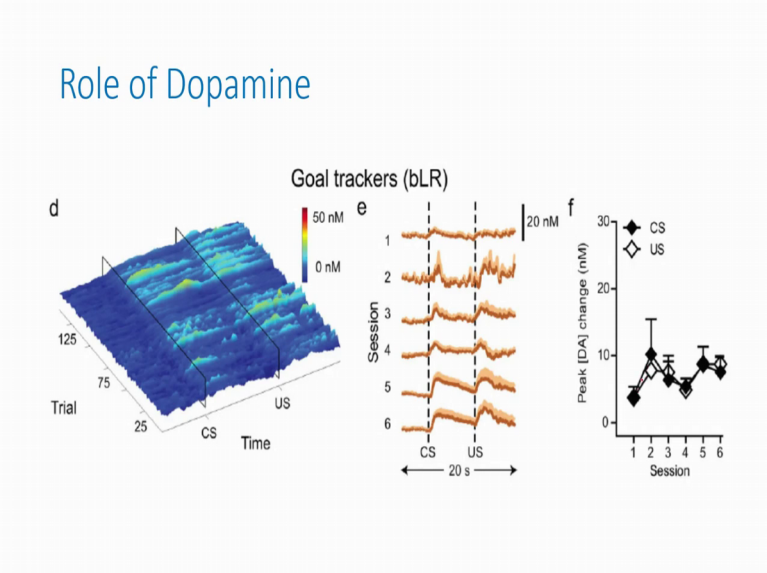

What do we see if you look at the goal trackers here. So, the goal trackers when we look at it on the other hand has a very different behaviour look at that US region right and the CS region they develop this amplitude equally for both of them they need the dopamine the ink they show an increase in the dopamine release for both the CS as well as the US. So, these are the low responsive animals low response breed they are goal trackers we have seen them.

Now, we are going into their brain and measuring their levels of dopamine while they are actually engaging in a task. While they are actually learning how to perform in the task in this task and what you see is that for both the CS and the US the dopamine is increased. So, this against the sign trackers where we see the US I mean the dopamine increase to the US goes down alright. So, that is what we characterized here too now its very strikingly different when I comes to the low responsive guys, but what you also

want to note is that the basal level of dopamine two. So, they are starting it over. So, this would be around 12 nano molars or something around and they go up all the way to about close to about 20 nano molars good.

Now, how about these guys they start much much lower all right. In fact, the peak of their dopamine release is the basal level of this guys ok. And in fact, the basal level is even slightly more its 12 nano molar. So, these guys peak is less than the 10 nano molar even if you give and take at the best their peak response corresponds to the basal response of the high response basal concentrations of the high response breed.

So, what we have done now is that we have tied this complex behaviour seemingly complex right you the behaviour that tells you whether somebody is impulsive or not a behaviour that tells that somebody's sign directed versus goal directed a behaviour that tells that somebody is very very locomotively active alright. All of this we tied together and say that can be traced back to there levels of dopamine that gets released while you are engaging in the task.

In effect what it means is that what is it rewarding and what is it actually making you learn in the sign directors the act of responding is good enough to release their dopamine, while for the goal directors they need their food it does not matter there they are for the food they understand clearly they need to respond ok. So, that does serve us very good reward mean you want to actually if there is a signal that you want to actually be able to learn that you need to press the lever.

But that is not sufficient they need they also learn its the food and that is going to actually give me more dopamine release. Now you can say this is all good, but this is all in a to breed of animals that been laboratory bread that is been heavily in bred you generated these two kind of lines and said hey look they are high responsive and they are doing this they are doing that and then you go ahead and measured dopamine levels and what is a big deal here.

Maybe its an artefact of the way how you have selectively bred them, even then it is interesting because you can actually bias the behaviours by selective breeding. And all that stuff apart from this the impact of that a study becomes even more higher simply because, they perform these kind of classification on a completely out bred animals right animals that are routinely used there are no selective breeding here. So, they completely

out bred take a general population take this general population and then classify them into sign trackers versus goal trackers how do you do that you put them through this behaviour that you can that helps you to classify them into sign versus the goal.

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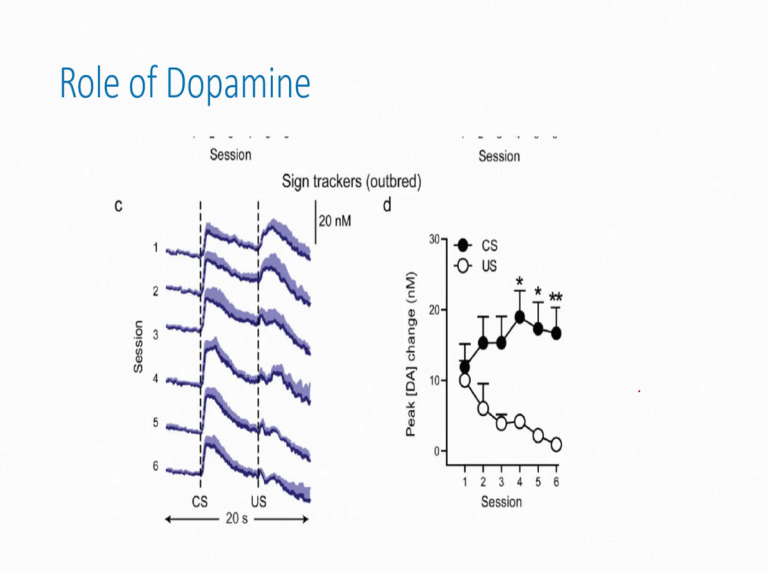

Then go ahead and ask how are their dopamine responses right please note its sign trackers outbred all right. If you are interested you can actually look at the behavioural data that is present just before this figure in the paper. You are looking at the sign trackers and what did we see in the out bred animals the response dopamine response to the US falls down while the CS goes up, it is even more prominent here. In fact, the US responds if at all anything here is pretty clear and then that completely falls down to almost no response at all ok.

Now, that is what this levels are you remember the 10 nano molar number that we are talked to you about that is about baseline and from there it comes down to the US. So, the US is no longer rewarding for them that is the key here, on the other hand CS by itself is rewarding it is not just the CS by itself is rewarding US is no longer rewarding its just actually down compared to goal trackers.

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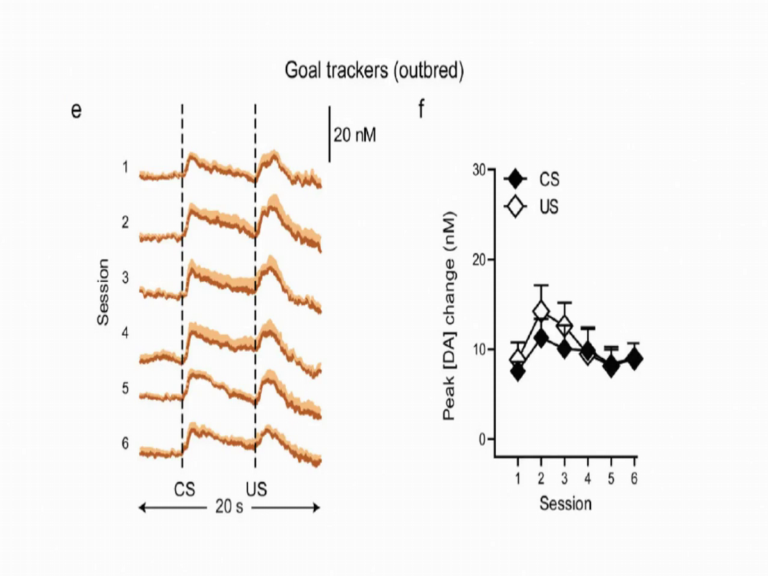

These are starting at the same level its out bread its about 10 they go up and then they equilibrate to that same level all right. So, in a longer run they really does not it does not matter at all. However, what you see is that very very interesting you see a steady response for the CS and the US all throughout. In fact, the amplitude of that peak goes down as indicated by that initially. So, you can see it here initially at some level you are actually increasing it, but then that level of increase kinds of kind of tones down, they kind of get used to the fact; if this is the thing that I need to do and that is what I am actually doing and I that this is the thing that I am supposed to get if I do this and that is what exactly I am getting.

So, these guys we call them as the guys who are cognitive in their response they where measured that they know that they are pressing the lever to get the food. While in the other guys the response that we have acquired is very reflexive they are pressing the lever because there is a stimulus and that by itself is rewarding alright. So, this is good in terms of classifying them as cognitive and reflexive can we actually test them behaviourally too how do you do that one of the thing that you want to do is that you want to ask can we use these acquired responses in a second order conditioning can you actually make them associate this with the other stimuli.

And if they actually wanting to do this more right that is the idea here right the we talked about that the reflexive response in the sign trackers is sufficient for them to actually a

trick them as a reward right. If they actually think that is the case then they would like to or they would want to do this behaviour right that is the point right. So, it is not as if that they cannot associate the fact that ok, its not come they just think that if I keep pressing I will get it, its not that its just they wanting to do that response how do you go ahead and prove it.

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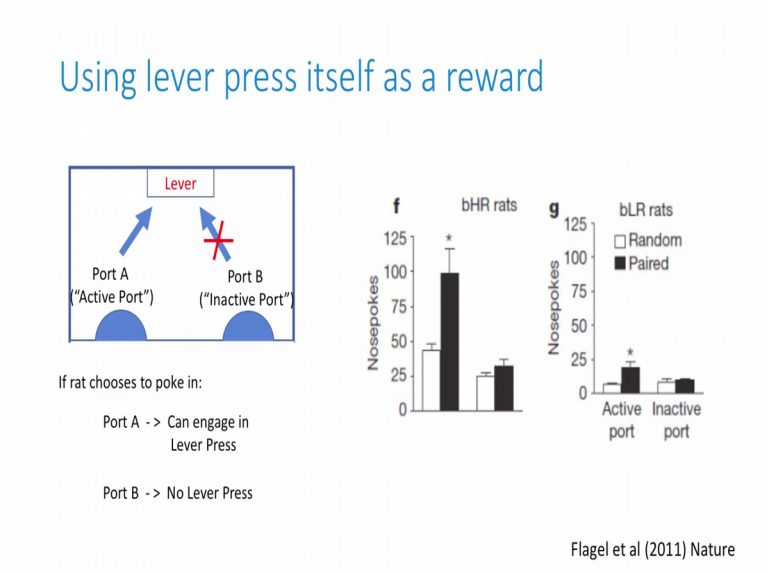

So, for that they do something called as a second order conditioning experiment where they take these animals and then they say they offer them two ports; one let us call it as an active port and then other is called as an inactive port. The port is a hole through which the mice can actually insert its nose or the nostril or the rat can insert its nostril. In an active port the insertion of the nostril actually presents I mean presents the possibility of the cue and then the food and so on and so forth, but the inactive port is not cannot I mean it is not associated with anything. So, it does not doing the rat does not have anything it does not sign signals anything at all.

Now, what you can do is that you can ask if lever press were to be. So, much want wanted by this animals can I make these animals learn that only if you poke into this active port you would get the ability to press the lever versus the inactive port if you just go into there then nothing happens the point they did that study. And then the point is the beautifully learned this they actually both the sign trackers and the high responsive element high response the goal oriented guys learn it.

However, the differences the sign trackers learn it much much more faster than the gulf oriented guys and they also do it more frequently illustrating the fact it is not just some dopamine levels and some hypothesis of they wanting to do it. But you can actually see them doing something else to get the opportunity for engaging in that sign tracking clearly demonstrating that what we have been hypothesizing that the stimulus response itself that act itself is good enough for them or incentive enough for them to be engaging in.

With that I hope that I am able to convince you that we can track down these complex behaviours down into single molecules and their fluctuations. And in doing so, we have learnt quite a bit about the reinforcement learning or operant conditioning per se. And in the next lecture and lectures what we will do is that we will revisit this idea of what do we learn in this stimulus response outcome briefly and then summarize clearly what exactly is possible hypothesis of what is happening in the brain.

Now, we come to the point of asking questions in the brain what is happening in response to learning. So, we step back in our lecture and then say see what are all the things that happened in the neuroscience of memory and that we will go into that literature little bit before combining this behaviour to the tough the neuroscience of memory as we promised in the course.

Thank you.