What I'm going to be talking about is some of the fundamental work that has been done trying to understand neural basis for memory and spatial perception and cognition that comes largely from behavioral and electrophysiological studies in the brain system that's shown here-- the hippocampus. And as I was mentioning before we started, this year's Nobel Prize was given to John O'Keefe, who discovered the properties of individual neurons in the hippocampus by applying these methods for recording the discharge of single cells by putting little wires into the brain-- so-called extracellular recordings.

You put in a wire. The tip of the electrode can record electrical discharge of cells. You measure the discharge of cells as animals move around in space. And you try to figure out what this part of the brain does.

Now where the observation part of science comes in in this case is interesting, because it relates to another aspect of neuroscience. And that is the relationship between the neurobiology and behavior. And this is an approach known as a neuroethological approach. And that's studying the brain systems in the context in which they actually evolve and were used.

And so that could apply to the use of song as a mechanism of communication in birds. It can come from the finding prey in the dark, when it comes sound-localization owls. In the case of rodents, O'Keefe appreciated the fact that the hippocampus in rodents really has a primary role in spatial navigation-- that animals that have damaged the hippocampus have problems with spatial navigation. And the hippocampus had been studied up to that point using animals that were head-fixed.

So you take a little rat. You fix his head. And the reason for fixing its head is for convenience, largely, so that when you place these little electrodes into the brain, the animal doesn't move. They don't move. Electrode moves, you can't get good recordings.

So you need to keep the preparation fixed. So you fix the animal's head. Then you figure out ways to actually look, to study the system given the constraints of the methodology.

And that involved, largely, before John O'Keefe in 1970, using methods of classical conditioning. So you might be familiar with basic learning theory. And how do we learn how to do things? Well, it's basically chaining together stimulus response associations. You see something, you do something, you get rewarded for doing that. You're

more likely to do that again in the future.

This is a basic Pavlovian conditioning. I ring a bell, you get food. You associate bell with the food. And so that was the thinking-- that all of cognition can be built up from basic stimulus-response associations.

But there was a movement around the time that O'Keefe was doing this work that proposed that that was insufficient-- that simple behavioral simple stimulus response learning was insufficient, that there was some kind of internal foundation upon which learning was applied. And this was the so-called cognitive theory of learning and memory. And the hippocampus was posited beta-site of one property of this cognitive learning as applied to space.

And the observation was actually a fairly simple one. If you take a rat-- I see you want to learn something. That is, if you want to learn to associate a cue with food or you want to train it to go over and press a lever for food or-- you want it to learn something, and you do this in an environment and put it in a box. Well, if you take a rat and you put it in that box, let's say, the day before, and just let it wander around. It does nothing. It just explores space. You take it out. And now we take two rats-- one that's been in the box before and one that has not been in the box before-- and the rat that has been in the box before will learn faster than the animal has not been in the box.

And you say, why would just passive exposure to that box enhance it's learning? And this phenomena is known as latent learning. The animal had learned something that it could then apply to this new learning even though it was not instructive. It wasn't rewarded for doing anything, it just explored. And so this idea that there was some sort of latent capacity to enhance learning was motivated the study of the hippocampus in the context of non-head-fixed recording.

And so it keeps real inside. In fact, the paper that was cited for the Nobel Prize was the paper in which he first recorded from these cells-- and all he did was just take the animals out of the ear bars. So he took the animal out of the ear bars and just let it run around on a tabletop, just like this, actually. It was a table at the University College London about this size where the rat just kind of wandered around. And he made observations-- oh, here's a cell that fires when the animal goes over to the left hand side-- very descriptive, but the key insight was to study the hippocampus when rats are doing what rats normally do-- explore in space. So it was this ethological approach.

And what he discovered was that cells in the hippocampus.-- and this is a cross-section. The hippocampus is found here. It's in the medial temporal lobes. The name hippocampus comes from the Greek for seahorse, so in humans, it sort of looks like a seahorse. The regions here-- the terminology CA, these different fields of the hippocampus, comes from cornu ammonis, or Amman's horn. That's because it looks like a ram's horn. So if you

think about it, it's like little ram's horns right here, put them in the temporal lobes and you move them in there, that's where your hippocampus is. Just like this.

And if you make a cross-section, slice through that, this is the circuit. So information comes in from across the brain, converges in the primary input to the hippocampus-- that's called entorhinal cortex, which is what the other Nobel Prize was awarded to-- the husband and wife team that had discovered and identified the properties of cells in the entorhinal cortex, these so-called grid cells that seem to carry information about actual, it seemed like, Cartesian-like spatial information conveyed in the hippocampus. So stuff comes in from the rest of the brain, converges in the entorhinal cortex, and then goes around this little loop, from these three primary subfields-- the dentate gyrus, CA cornu ammonis 3, CA1, subiculum, and back on again. So it goes through this loop. Classically, it had been referred to as the trisynaptic loop. One synapse, dentate, CA3, CA1, and then back out.

And again, recordings in this part of the hippocampus reveal the properties which I'll mention, and that is that the cells respond to locations in space. But prior to that-- this electrophysiological work in rodents-- there had been human neuropsychological work, in particular the seminal case of the patient HM who had been studied here for many decades before he just recently passed away. Known as HM, or Henry Molaison, as he is sort of recently revealed to be a patient who had undergone bilateral resection of medial temporal lobes. Cut out parts of his hippocampus and other associated medial temporal lobe structures to treat intractable epilepsy. He subsequently lost the ability to form any new memories. So had permanent anterograde- couldn't form any new memories going forward in the future and lost some of his older memories.

So you lose memories in humans, rodents can't navigate in space, also humans have a spatial deficit, so there's some connection between space and memory. And the question is, what is that? What would link spatial navigation and memory? But not just any kind of memory-- what we refer to as episodic memory-- memory for events or experiences. And so the working hypothesis is that these two things are really connected by a need, a computation imperative, to maintain information about time order. And that is, if you're going to use experience to guide future behavior, you need to figure out what the causal relationships are between events in the world.

If I see A and B, what I really want to figure out-- I don't just want to record the fact that A and B happen together. Ultimately, I want to try to understand the relationship between A and B. Did A cause B, or how might I actually predict B given A? And the way I would do that would be to construct some kind of simple internal model, a predictive model, that's based on experience. And so the idea is, hippocampus captures experience, and then sort through some process, which we'll refer to as the process of consolidation, translates experience into some working model that can predict events and can be used to guide behavior in decision making. And critical to that is just the idea of time and a particular time order.

So as I mentioned, the use of very simple technology, in this case extracellular neurophysiological recording-- taking a tiny wire-- this wire is actually four small wires, each one about 10 microns across. You twist them together in a little bundle. The bundle is about 35 microns. Human hair is on the order of typically about 50 microns, so these are wires, or multi contact electrodes, about as large as a human hair. We thread these things through the little oil rig drilling device here, which is-- these little micromanipulators allow this wire to be driven down through very small guide cannula, and so out the bottom will be a number of these independent individual electrodes, each controlled by their own micromanipulator.

So we can send these electrodes down-- this entire device, in this case, weighs anywhere from 12 to 20 grams, and this can be placed on an animal's head permanently or chronically, and that is that once it goes on, it doesn't come off. So they will have this little helmet like thing on their head, a small opening is made in the skull, the wires are sent through, and the whole surgical procedure takes maybe 30 to 45 minutes. It's like an outpatient thing. It would probably take longer to have your wisdom teeth pulled than to have a brain implant installed. But then once this is installed, these electrodes can be driven down and placed permanently. It gives you the ability to monitor pattern activity across large populations over long periods of time-- days, weeks, months. So you have tapped into activity in this brain area, and you can monitor as animals experience, learn, and recall.

This is what the raw data looks like. This is a cartoon of the electrode with four contacts. The idea with the four contacts is it gives you the ability to triangulate location, much as you stereoscopically can determine depth. These four contacts will give you the ability to triangulate things in three dimensional space.

One of the properties of this hippocampal circuit, and that is-- so this little cross-section-- you imagine a neuron here. And so there are going to be, again, neurons distributed across the hippocampus. In the rat, there are on the order of maybe 200,000 cells in area CA1. In the entire hippocampus, there are on the order of one to two million cells. And if you drop an electrode any place into the hippocampus, you will find cells that have this kind of spatial property. And so what that says is that spatial information is distributed not in a topographic way. In other words, it's not one location in space is mapped into one location in the hippocampus.

Unlike some of the sensory areas that have this kind of topography, for instance, if you record in the visual cortex, where there was there would be some correspondence between location and visual field, and the location of cells in the cortex that respond to that so-called retinotopic mapping-- visual field mapped onto the anatomy. Same thing with the somatosensory system. As I move and I touch different parts of the body, the cells that respond to that will be mapped out in a largely one-to-one correspondence between the adjacency of stimuli in the input space and adjacency of the representation in the neural space that does not occur in the hippocampus. Two cells that are right next to one another are no more likely to respond to nearby locations in space than two cells that are distant from one another.

So, as we'll discuss, the principle of information representation in the hippocampus appears to be one of kind of sparse distributed patterning, that you have lots of cells that will respond to different environments and individual cells don't have a unique relationship to locations. It's really the pattern across cells that gives you a unique signature of code.

We're taking advantage of the fact that you don't necessarily have to place the electrodes at the proper place in order to get responses in some location in space. Anywhere you put these electrodes in the hippocampus, you're going to get a certain fraction-- generally about 30% of the cells will respond in the given environment. And this is what those responses look like. I won't go through the technical details, but, needless to say, this just shows how events, action potentials that are detected-- in here, you see a voltage trace, you pick out the amplitude of these little voltage transients generated by action potentials in the cells, you plot the amplitude across these different channels. In this way, each point is an action potential, and what you see is that the amplitudes will cluster in a way that reflect the relative position or location of cells-- the sources relative to these wires, using the basic principle that if you're closer to a wire, the signal is going to get stronger. So amplitude is essentially inversely related to distance.

So here, this is the amplitude of an action potential plot across two channels. These points are larger on channel one, small on channel 2. That means it's close to channel 1, far from channel 2. And then different cells will have different relations. This will be large on channel 2, small on channel 1, et cetera. So you can figure out where these cells are in space, means you can pick out lots of cells from, in this case, maybe 12 to 18 electrodes can give you 50 to 100 or more cells.

And then looking at the activity of those cells in a simple box-- this is just a little box, one wall removed, little ceiling of cubes, simple architectural design, nice, clean and simple-- what you get is clean and simple mapping of spatial locations into these neural responses. So each one of these panels represents the activity of individual cells. So this is about 80 simultaneously recorded cells. The color of the heat map indicates the firing rate of these individual cells. Red indicates high firing rate, blue indicates no firing. So this is a top down view of that box. So this cell, for instance, when the animal is wandering around in the box, the cell is silent in all the blue areas, and when it goes in the lower right hand corner, the cell fires vigorously. So silent, fires vigorously. This one fires on the left hand wall. This one also fires on the lower right hand side.

So this points out the combinatorial nature of this spatial representation, and that is that if the animal is in the lower right hand corner of this particular box, we'll get these two cells to fire. If I take the animal and I put it into a different box, all of these responses will be scrambled up. There's nothing that says this cell will fire in the lower right hand corner of another box. And certainly, even if it does fire in the lower right hand corner, this other cell

isn't going to fire along with it. And at any given location, there are roughly 1% to 5% of the cells that are firing. So at any given location, there are about maybe 5,000 cells in the hippocampus that are active. So the unique location and unique context and environments can be conveyed across a unique pattern of about 5,000 cells out of 100,000 or 200,000 cells. So there's large combinatorial space in which one can represent unique locations or potentially even unique experiences within different locations.

You see that many cells are silent. On average, about 30% of the cells respond in any given environment. The silent cells, as we'll see, they can be detected when the animals are not in a running around or experiencing space, but when they're asleep or in these other offline states, when the hippocampus is actually thinking about other stuff. We'll talk about that a bit. And then here, you can also see a small number of these cells. In this case, about 5% to 10% of these cells seem to have elevated firing rate across the entire space. These are actually a different class of neurons. These are excitatory neurons. These are inhibitory neurons. The inhibition, the idea that you have circuits that can both excite and inhibit, and that this is used as a circuit property to sculpt computation is something that we'll also discuss.

So there's balance between excitation as kind of a circuit principle that's used. Inhibitory cells fire all over the place. They're not really communicating information. They're really modulating the processing of information. And another property of these cells that O'Keefe termed place cells is that when animals are constrained to move along these limited paths-- in this case, this is a linear track, as we refer to it. It's like a little corridor, and it was moving down this corridor. When they move down a corridor, cells don't only fire where the animal is, but also in the direction that it's going. And so this is the first indication these cells are not just-- again, it's not just a GPS. It's not telling you where you are. It's at least telling you where you're going, maybe what you're doing.

So here, if I look at this yellow cell, I can tell that the animal is not only in this location, but it's moving down this linear track in this direction. So there's going to be a unique sequence when the animal walks along this path-- yellow cell, red cell, green cell. So the different cells are color coded here. So if you look over time, you'll see that there will be a unique sequence of activity in the hippocampus that reflects the animal's actual behavior experienced in that space.

So here, this is just a little movie that shows raw-- this is what you would actually see if you're running the experiment. This is a little top down view. The green circle just highlights where the rat actually is. The color coding-- these are the cells that we're picking up over here. This is data as it would be coming out of a set up. You see, this light blue cell fires here, the dark blue cell fires here. Dark blue cell, light blue cell. So this is the spatial firing property, place cells.

So the animal has stopped. The one thing you will notice-- you saw lots of activity, and animal stopped there,

there was this big burst of activity. He'll stop again a little bit later. Now he's moving. Now when he's moving , if you listen carefully, you'll hear that there's this background rhythm. There's a modulation that's going ch-ch-ch-ch. Background modulation activity which is associated with locomotion.

So there are really two modes-- you're actively engaged or when you're taking information in, you get this rhythm. When you're inattentive, not engaged, not taking information in, but internally evaluated, the rhythm goes away and is replaced by these bursts of activity. And so these two modes, active attentive-- you're processing information coming in, inattentive-- you're evaluating information, you're thinking about stuff-- can be reflected in these two characteristic modes, which you can literally hear. You can hear the difference between the two.

Obviously, I've been listening to these things for a long time so it's very easy for me to pick up. It might be harder for you but, you listen to it a little bit and it's very easy to distinguish these two different brain routes.

So this is going to be another view of that data. So same data, only now, instead of showing you the raw data, where is the firing. And that's one thing about this correlate that's so compelling. That was literally raw data as it was coming out. There's no processing at all and you could see the correlate, you can see the spatial correlate, which tells you, this is not something that requires I have to do multiple regressions, and show you all of the-- give you some sort of statistical confidence that this is what the hippocampus is doing. You can literally see it in individual cells.

The spatial correlate is extremely robust, compelling, and consistent. Those cells weren't selected. If you record any of the cells in the hippocampus, they're all doing that. The estimate is that over 95% of the cells that you can record in rodent hippocampus will have these spatial properties. So it's really a fundamental property of this memory system.

So this is the same data, except now, instead of showing the spiking, we're going to use this simple Bayesian Estimation Algorithm to ask the question. "OK, if we know which cells are firing, can we guess the location that the animal would likely be?" That is, if we know the firing as a function of location, we can use a Bayesian inference to guess the probability of location, given firing.

And that's what we're going to do here. Just asking, if we know which cells are firing-- for instance, if the blue cell is firing, you would say, "Oh, the animal's probably over here." So recording across, looking at pattern across many cells, and then we're coming up every 100 milliseconds, we're coming up with a probability that that pattern could have occurred if the animal was at any location on this track.

And the probability is going to be shown by a triangle. Big triangle means high probability. And what you'll see is, when we do this estimation, when the animal's moving, you see the triangle. The triangles are only highly

probable when the animal is actually moving, and only at the location that the animal is. So the hippocampus is centrally-- the hippocampus representation is tracking the location the animal and also when the animal stops.

Now, if you listen, you heard the burst and you look at the triangle, when the animal stops, the triangle no longer corresponds to where the animal is. In fact, when you get the burst, you see the triangle jumping around the track. So again, there's these two modes and the representations have these two properties. Moving, oscillation, track current location. Stopping, oscillation goes away, representation now jumps across the track.

And interestingly, these little bursts, like that, also occur, not just when the animal stops briefly, but when it actually goes to sleep. So here on the inset, this is the animal now has been taken off the track altogether. It's just sitting in a little box somewhere else, it's curled up, and it's asleep. You get these same bursts and when you decode activity, you find you can decode the position on the track and, if you look carefully, you see that the position actually follows a sequence of trajectory along the track. And we'll go into that in a little bit more detail.

So you think of there being these two states, the offline and the online. And the online, when the animal's moving, the characteristic mode of activity in the hippocampus is an oscillatory mode, described as the theta rhythm, which is this 10 hertz oscillation. When the animal stops and becomes quiet and immobile, within about half a second, oscillation goes away and is replaced by these large transient aperiodic events, these so-called sharp waves, because in the extracellular electrical field that you measure, you see these large deflections. And then, if you zoom in-- I'll also show you shortly-- you can actually see that these very high frequency oscillations, about 100 to 200 hertz, riding on top of that, these are referred to as, ripples. And this is the term that Gyorgy Buzsaki came up with. He described this sharp wave ripple activity as corresponding to this offline state, quiet wakeful, and some sleep states.

So the first thing is to look at this oscillatory state. So an animal's actually moving. And I've already shown you the spatial correlate, these place cells. But there's another property of these cells that O'Keefe also discovered. But this was in early 1990s, around 1991. And that is, he noted, if you actually look at the discharge of single spikes with respect to this oscillation, first of all, the spikes are actually phase locked. In other words, here spikes fire when the oscillation, this theta rhythm, is at its peak. So the idea is, this oscillation really reflects time varying excitability, sometimes where cells likely to fire, other times when it's not. And you can think of this oscillation in excitability as being an oscillation in relative excitability, or inhibitions. So inhibition, elevation is high, it's low, its high, it's low. When inhibition is low, cell fires. When it's high, cell doesn't fire. So this is modulation excitability. You see this here.

But he noted another thing, and that is, if you look at the precise phase-- so here, yes, cells tend to fire at the peak, but here, this is now over time, but animal moving at constant velocity, space, and time, are

interchangeable. So as the animal's moving through it's place field, the spikes start to fire earlier and earlier, as this phase code, spatial location. So you can tell, based upon the relative phase, whether the animal is just entering the field, spikes fire late, here close to the peak, versus further into the field, where they fire a little bit earlier. There's a relationship between distance into the field and relative phase. What he termed, phase precession.

And this is a representation of that. This is actual data. This is just a cartoon that illustrates the basic principle. And so the idea that, if I have a place cell, if I look at the marginal distribution as a function of location, this would be the place field. Otherwise, it would just collapse all of this. This is the spiking now, as a function of position and phase. If I just look at spiking as a function of position, as just the density of firing, what I would get is a place field. Not many spikes here as the animal enters the field, lots of spikes here as you get into-- this would be the classic spatial receptive field.

But now, if I introduce phase, as well, now you say, "Oh, wait, there's a systematic relationship as well between phase and location." In fact, phase is a better predictor of relative location than firing rate. If I asked, when did the spike occur? If it occurred here, late in phase, then I know the animal is just entering the field. If it occurs early in phase, I know it's at the end of its field.

And that's interesting. And this is a simple model that says, well, an easy way of explaining that is, if you just have this excitability model-- and this was one of the questions that I guess you asked about this sweeping inhibition. So if we just imagine that you have an input, excitatory input, shown in blue, and then an inhibitory input, shown in red, where the inhibition is oscillating, and you apply a very simple biophysical model that says, a spike action potential is going to occur when excitation and blue exceeds inhibition and red. More excitation inhibition, you get a spike.

So here, in this oscillation, anywhere the red trace is higher than the blue trace, no spiking. So in this case, when excitation is low, you have to wait until inhibition drops all the way to here to get a spike. This is late-phase. So weak excitation means you have to wait until inhibition is low. So this is the sweeping inhibition, you have to wait until it's low. When excitation is strong, I don't have to wait so long. It can fire earlier. So the principle here is that there is a relationship between magnitude and latency. Stronger means earlier. That's the biophysical principle. Very simple. Stronger earlier, weaker later. That will give you this phase precession property.

Phase precession, you might think of as this biophysical curiosity. But when you think about how that would apply when you have more than one place cell-- in fact, I have two place cells here, one in blue, one here in purple, where place cell one is to the left of place cell two. So as the animal's going through here, first the blue cell will fire, and then, the purple cell will fire.

And if you look at the excitatory drive, shown here as a ramp in blue, ramp in purple, and now you ask, "When is the blue cell going to fire, and the purple going to fire, during each one of these oscillatory cycles?" The answer will be, well, because the blue's-- the excitatory drives the blue cells higher than the purple cell, blue is always going to fire before purple. In fact, in each and every cycle, it will be blue purple blue purple blue purple. So this principle of phase precession, or phase coding, for single cells, actually gives you sequential encoding across a population that you will actually on each and every cycle have a sequence. The code in the hippocampus is not a location, it's actually a sequence, a trajectory.

This is just raw data, but I'm going to quickly go-- this is just talking about what the spiking looks like. And you can see, if you look at it, you see these spike sequences. But the property's more clearly demonstrated when I do this decoding. So what I'm showing you here-- this is, again, raw data. But now, instead of showing the spiking, I'm showing you that the result of doing this decoding, this Bayesian decoding, where there's a probability estimate that given spiking activity in each one of a set of successive 20 millisecond windows-- so I'm walking along, now I'm firing at a finer temporal resolution every 20 milliseconds. I'm doing the same decoding, probability is indicated in grayscale.

So you can see here the dark areas, this is high probability that this pattern-- the animal would have been in this location, or to get this pattern of activity in this 20 millisecond bin. And so, what you can see here is that the probability, these Bayesian decoded probabilities, form short sequences every single theta cycle, what we refer to as theta sequences. And the theta sequences actually move from just behind the animal-- dotted line is where the animal actually is. The estimate goes from just behind the animal to just in front of the animal. So 10 times a second the hippocampus is actually expressing a representation of spatial sequence that goes from behind to in front of the animal. You can think of behind and in front as also reflecting recent past and near future.

So there is this relative predictive differentiation of response as a function of oscillatory phase. So if I want to look at, "Gee, where did I just come from?" I just have to look at activity here, at this slightly earlier phase. If I want to ask the question, "Gee, where am I likely to go to?" I simply have to shift the phase, the channel that I look at here, and I can see where the likely future location is.

So you can think that there is actually a code, not just of location, but of the relative causal relationship between locations mapped into phase. And we'll see that we can experimentally test this idea, that that's just not an artifact of our decoding, but the animals are actually using information of these different phases to drive spatial navigation in particular ways by using some of the tools for manipulating activity in a closed loop optogenetics. So we see we can manipulate activity, specifically manipulate activity, hippocampal activity, different phases and show these different phases actually carry different functional consequences.

So we've got these sequences. So we've got these sequences captured during these oscillations. Are these things actually meaningful? Well, some of the indications that, A, the oscillations in the sequences are meaningful first come from the observation that, as I mentioned, actually successful, using memory-- information that the hippocampus requires that you actually communicate this to executive structures that can guide behavior, make decisions.

That would include the prefrontal cortex. The portion of the prefrontal cortex, which form part of this limbic circuit, referred to as the limbic prefrontal cortex, which have direct connections from the hippocampus. These structures are-- in the hippocampus, you have deficits in spatial learning memory. Prefrontal cortex-- you think of this as deficits in working memory and retrieval, executive control, decision-making.

But you can think of these two things as working together. Hippocampus providing information that the prefrontal cortex can use in order to direct behavior and decision-making. And you damage either one of these things, animals, rats can't find their way around the space. You damage either one of these in humans, you're going to get memory deficits. Dementia is-- when you think of dementia as being problems of cognition and memory, you can get them temporal lobe dementias, frontal lobe dementias, you can have-- they're really very closely related.

And so we can look at a simple task. This is a simple task, testing a so-called working memory. Just remember, what did you do last? And this task, it's just a simple alternation, where you turn left-- first time you turn left, next time to go right. Ethologically, it's like, "Look, I just got food over here, why don't I check out the other place? I'll check out places where I didn't get food." It's a so-called win-shift strategy. I got something here this time, I'm going to go someplace else. As opposed to-- a reference memory strategy would be referred to as a win-stay. That's really a good spot. Home. I love going home because I've got my TV, I got my microwave, I'm going to stick with that place. Win-stay, you keep going back to the place that rewards you.

And so you can think of both-- again, both of these things have ethological value. Home is a good place, that's a reference place. If you're foraging, win-shift, don't go back to the place I just looted, right?

Again, these two structures-- classically, you think of-- in the prefrontal cortex we think of working memory cells. And this is the short term, the idea of short term memory. So prefrontal cortex typically has been thought of as subservient. Working memory, where working memory is about holding information over short delays. It's an overlap in terminology, where working memory in the prefrontal cortex is really thinking about time. Working memory in hippocampus is really thinking about the context in which it's used, relative, session specific information, trial specific information.

So I'm not going to go through the details. You have these two systems. One interesting property, if you look at these two systems simultaneously, what you find is that the same idea about oscillatory phase governing the firing

of cells in the hippocampus also applies in the prefrontal cortex. That is, cells in the prefrontal cortex like to fire at a certain phase of the hippocampal theta rhythm. They care about, their listening to, this rhythm in the hippocampus.

And so, we can look at a task. This is basically the same kind of task, only now there's a back-to-back T-maze. So there can be two T-mazes, and we're just going to do a simple variation on that, on that working memory task, in which the animal's going to start from one of these two arms-- it's going to walk down this arm and then, it has to go to the arm that's on the same side as it started from.

So it has to remember, "Where did I start from? Oh, that's the side I have to go to." Then it's going to turn around, it's going to come back, run down here, and then, we're going to force it into one of these arms. So two back-to-back T-mazes. In this direction, the animal chooses, in this direction, we choose. In this direction, there's a working memory demand. It has to remember where it came from. In this direction, doesn't have to remember anything, doesn't make any difference. So behaviorally, it's symmetric, but cognitively, here there's a working memory demand, here there's not.

And then we're going to look at all these things, oscillations, spiking, and the oscillations, look at the peak time, look at the firing with respect to that, firing, spiking, as a function of this oscillation in both structures. The bottom line is what you find is, that this is a measure of relative phase locking and as how well do prefrontal cells actually lock to this data oscillation.

And what you find is that the degree to which they locked the theta rhythm is a function of whether or not the animal has to choose. So the red ones are when the animal's going down the arm and it's got to choose. The gray one is when it doesn't have to choose, when we choose. Then in addition, the solid red is when the animal had to choose and it got it right. And the stipple red is when it had to choose and it got it wrong.

So the degree to which the prefrontal cortex actually locks, successfully locks, to the hippocampal theta rhythm, predicts whether the animal actually makes the correct choice or not. So it's as though this is a channel that is necessary for effectively communicating information between the two structures. And, that not only is it in the blocking of the spikes, spikes in the prefrontal cortex, the rhythm in the hippocampus, it also comes in the blocking of the rhythms themselves. So you can think of there being-- this is the theta rhythm that you can detect in the prefrontal cortex and in the hippocampus. And what you can see is there are two conditions. One, the animal's actually choosing, is running down here, it's making a choice. And in about the half second before the animal makes a choice, you see these two rhythms actually lock, they become coherent. So transient coherence is predictive of correct choice behavior.

The thinking is that the rhythms themselves can be generating coordinated through the regulation of these local

inhibitory circuits. In fact, there's been a lot of interest, for instance, in the relationship of local inhibitory control and neuropsychiatric disease and disorders. So, for instance, disrupting local inhibitory rhythms. In particular, some, for instance, the theta rhythms in prefrontal cortex can be associated with disorders like schizophrenia, for instance.

So the inability to effectively impose these modes and then synchronize these modes can introduce disruptions in the ability to communicate or use memory. Cognitive disruption coming through disruption of these oscillations through disruption of inhibition in these local circuits.

Now how you actually coordinate these two subjective states. We've been looking at the role of mid-line thalamic nuclei. So the thalamus as being a set of structures that have widespread connectivity to all these cortical areas, that much of their connectivity is inhibitory, and so they have the ability to actually coordinate, modulate and coordinate, these oscillatory modes.

We've even just recently published on individual cells we found in some of these mid-line thalamic nuclei that, for instance, will branch. Single cells will branch and target cells in the hippocampus and the prefrontal cortex. So they would be ideally positioned to introduce, to select and impose, this synchronization there. So that's the way we think about a lot of this dynamic connectivity being established, presumably through some sort of thalamic regulation.

And then, you think about the thalamus as being regulated by those so-called thalamic reticular nucleus that regulates the thalamus and it sets up these modes. And there's also a lot of interest now in the thalamic reticular nucleus in disease and disorders. A lot of the genetic screening has identified targets in the thalamic reticular nucleus.

So you can think about it again. It's like the oscillator in your computer or your radio that breaks down, you can't-- the information can be there, but you can't tune into it. So it's this fundamental tuning. You've got to have the modes and you've got to be able to lock to these frequencies. And then, beyond that, as we'll see, it's not just the frequencies, but it's also the precise phase within those oscillatory modes that carry different information. That we actually determine by taking advantage of these techniques, optogenetic techniques, for targeted manipulation.

So you infect the inhibitory neurons in the hippocampus with this optogenetically encoded and controllable channel so that we can optically excite inhibitory cells. So we infect this excitatory channel into inhibitory cells, and then, we can transiently, giving very brief pulses of laser light, we can activate drive, inhibitory cells, and then, because the local circuit, those inhibitory cells will inhibit the excitatory cells. And so we have about 20-25 millisecond control. And now, we can lock, or control, inhibition based upon the phase of this oscillation.

So the idea is, we're going to selectively disrupt, or inactivate, the hippocampus at different phases. We're going to ask, "Do those phases, do they differ in terms of their contribution to behavior and performance?" So here, we're going to lock inhibition to either the peak of the trough of this state of oscillation. And so in this task-- and we're going to do this manipulation, that is, selectively inhibit-- you're picking hippocampal output at either the peak of the trough, the theta rhythm, at two behavioral phases.

So in this task, animal's going to start on one of these arms, going to run up, and it's going to choose. So we're going to think about the starting arms as-- we'll refer to this as the encoding phase. This is where you have to keep track of where you are. And then, here in the central arm-- we'll refer to this as the retrieval phase. This is where you have to remember, "Oh, where did I come from?" And then use that to decide where you're going to go to.

And what we found was pretty surprising. And that is that, you might think, well, if you shut off hippocampal output, turn off the hippocampus, you're going to get an impairment. It's just like in the examples that I gave of suggesting hippocampal's prefrontal cortex. Most of those come from lesion studies. You damage the hippocampus, the animal can't find its way around.

So if you were to optogentically lesion, or turn off the hippocampus, you might imagine, OK, animals won't be able to find a way around. So you could ask, "This experiment is going to identify which phase, which behavioral phase, are most effective in disrupting performance?" But what we actually found was, when you selectively inhibit activity at different phases, you actually get an enhancement of performance. They get better.

And it depended-- there wasn't just one phase, a good phase and a bad phase, but both at the peak and the trough were both effective in enhancing performance, but only when applied at certain behavioral phases. In fact, there was this double dissociation. And that is, that trough stimulation, when applied here-- so when you stimulate in the trough, in the retrieval segment, animals got better. When you stimulate at the peak, in the encoding segment, animals got better.

So it wasn't that the peak is good or the trough as good, it's the peak. The peak is good during retrieval and the trough is good during encoding. So what it says is, the peak and the trough had two different functions. And if you actually think about what I was showing before, these sequences, these sequences that are going from just behind to just in front of the animal. What it says is, oh yeah, these different phases, peak and trough, you can think of as like past and future.

And so if I'm sitting over here in this encoding segment, what I'm really trying to do is I'm just trying to keep track of where am I right now. Now, I may simultaneously also be thinking about, oh, where am I going to go? But for this task, it's not really helpful. It's not really useful. At this point, I need to focus on where I am right now. So you

can think of simultaneously, the actions of these two channels, where am I, where am I going to go. And I can enhance performance by shutting off or inhibiting the non-relevant one.

So when I shut off the retrieval channel here in the encoding, I get better. It's like focusing attention. It's like, pay attention to what you're doing now. Stop thinking about stuff. Similarly, when I'm here in the retrieval segment, I'm also encoding. I'm trying to keep track of where I am as well as, think about where I'm going to. The thing is, keeping track of where I am here, it's not relevant for the task. It might be broadly relevant for the animal, but it's not relevant for the task. So when I shut off, I turn off that encoding channel, I'm able to enhance the retrieval information that goes out.

You might interpret this saying, "Oh, so this is how we can improve memory by selectively shutting off the hippocampus." Well, this is not a strategy for general cognitive enhancement. Hippocampus is working much better when all these phases are in operation. And that's because the hippocampus is not designed to solve this task. Hippocampus is designed to solve the broader task. It's trying to figure out how is this task relevant to all the other things that I have to do?

In other words, you're trying to integrate this information into all the other information you have. And that requires connecting the encoding or retrieval. You really need to have all of those pieces of information available. But it does point out that one can actually dissociate the function of information of these two different phases. The phase actually matters. And it matters at the level of high level behavior, decision-making. It's not just a idiosyncrasy or artifact of-- excitability is a function of phase. This is really how information is being used.