GERALD SCHNEIDER: All right. Let's get started. We have a little bit to finish up from last time with a few things on sleep. We were talking about sleep pathologies at the end of the last lecture, and we had a little more to cover there about brain mechanisms in sleep.

I posted a little announcement on the web along with the session on sleep that video of the sleep pathologist is in the [? Schering-Plough ?] if any of you want to see it. It's the narcolepsy section with two patients shown in video, one a dog and one a human being, a lady with cataplectic attacks.

You remember what cataplexy is? How could you summarize what's wrong in cataplexy? What's abnormal about it?

What happens to us when we go into dream sleep? We become totally paralyzed. Our muscles become relaxed. Well, if that state happens when you're supposed to be awake, it's rather incapacitating. It's often in people that have it with narcolepsy. It's usually part of narcolepsy. I'm not sure if it always is, but it's basically an intrusion of the REM sleep phenomenon into otherwise ordinary waking state. It's usually triggered by intense emotion.

We also mentioned a couple of things that were pathologies that usually kids have, but it's not really pathologies because so many kids have it, but then people get over it when they grow older. Nightmares are in dream sleep. Night terrors and sleepwalking occur in slow-wave sleep, which certainly proves that mental states occur in slow-wave sleep.

You don't need the electroencephalography of fast desynchronized activity to show mental images which occur in night terror and in sleepwalking, or even to show movement that's guided by a pretty high level of brain activity, and that people do organized things in the state of sleepwalking. My brother used to tell me that I tried to kill him when I was doing that.

[LAUGHTER]

How many of you have shown sleepwalking? Oh, fair number. What about nightmares? Well, has anybody had night terror, what I was describing? It seems to be more unusual. I probably have had it only two or three times. It's not always easy to distinguish from nightmares, but when you go through it the terror part of it is pretty similar to what occurs in nightmares.

But in nightmares, the dream-- it's an ordinary dream. It's just a terrible dream. In night terrors, it's not a dream. It's just a particular images that are associated with intense emotion.

Let's talk a little bit about brain mechanisms. It's been discovered that neuromodulator systems, axons with very widespread external connections, are important in controlling sleep and waking. They're important for other things too. And we'll be talking about those after we finish sleep later today.

We know there are axons like that, originating in the hindbrain, use serotonin as a neurotransmitter. They occur in the raphe nuclei. Raphe means the midline, OK?

The norepinephrine-containing axons, which originate in comparably small numbers of neurons, the best known group is in the so-called locus coeruleus, the blue locus in the hindbrain below the cerebellum. We'll mention that again today. And these axons go over the entire nervous system. They go down the spinal cord and go into the midbrain, deincephalon, and forebrain.

Similarly there are widespread acetylcholine projections. The best known one originates in the basal forebrain and goes to most of the neocortex, but there's also acetylcholine neurons with wide, pretty diffused connections in the hindbrain involved that we know now are involved in triggering REM sleep and then waking up.

OK. Let's just go over just some highlights of the work on brain mechanisms and sleep. One of the early studies-- well first of all, the transections, and then we'll go over [? notice ?] early studies of this, and then we'll talk about a few of these other regions. I want you to understand what these, in your textbook, they talk about these two types of transection, the [INAUDIBLE] and encephalocele. They just refer to transections completely through the neuraxis.

So encephalocele produces a spinal animal, but the investigators, they're calling it encephalocele because what they're studying is the isolated brain-- brain isolate. They're studying what's in front, instead of what's behind. Not the movement that the animal is capable of, but what the brain is doing.

And when you do that cut-- well first of all, I show it on the pictures you're more used to, this is where the encephalocele cut is made. Of course, if you do that, the animal will stop breathing and he will die if you don't support his life by artificial means, artificial respiration usually.

The other cut, it's called [INAUDIBLE], is through the middle of the midbrain. And it's shown here on the human. It's this one. It's often called the mid collicular cut because they usually go in front of the inferior colliculus and completely transect the brainstem.

So if you compare those two cuts and what the forebrain is doing, you make the cut back here, you find that the brain goes through sleeping and waking. The electrical activity shows sleep state part of the time, wake state part of the time.

But if you make this more anterior transection, the brain is asleep. It's asleep unless you electrically stimulate the midbrain. We'll talk about that later. If you stimulate in the middle of the reticular formation, you can wake the brain up, and that was the famous discovery that led to many studies of these systems of widespread projections.

Well, the results of those two transections, those were early studies had led to a focus on the hindbrain, as in where we have the mechanisms controlling normal sleep and waking, and that made people forget about the studies that had been there earlier, the lead studies of [? Noda. ?] And it's a complicated area. So if somebody makes a new discovery and the attention shifts to different things, and it's easy to forget about earlier studies.

[? Noda ?] was studying hypothalamus. And in the rat, he made lesions in the anterior hypothalamus and compared them to lesions in posterior thalamus-- pretty large lesions, but restricted to these areas, and he was a very good neuro anatomist. He became, after this, one of the world's best neuron systems neuro anatomist, and he ended his career here at MIT.

When he made the lesions in the anterior hypothalamus, he had rats with insomnia. They just didn't sleep. They slept very little or not at all. And animals with severe insomnia would eventually die if they couldn't sleep at all. He made the lesions in the posterior hypothalamus, he had hypersomnia animals that slept all the time.

Otherwise, the animals appeared to be normal. The animals with insomnia showed normal behaviors. They just became more and more debilitated when they couldn't sleep.

Since that time, some of the regulating systems have been discovered. For example, I mention that the raphe nuclei are use serotonin as a neurotransmitter, and they're very widely projecting. In the raphe of the midbrain and the hindbrain, they occur. And if you make lesions there, you can get insomnia, and how much insomnia you get depends on how many of those neurons you wipe out.

And the correlations are very good. The more serotonin axons you destroy by killing these cells in the midline raphe, the raphe of the hindbrain and midbrain, the less sleep you get.

And there are other studies that have supported that, that it appears to be a major regulation. How much of it works through regulating those systems in the hypothalamus is not very clear because in fact, the serotonin [INAUDIBLE] axons don't just go to hypothalamus, they go all over the place. So in fact, we don't understand that interaction yet.

Another fascinating study concerns the locus coeruleus region. Now, the locus coeruleus is where the norepinephrine axons are. But in the region of the locus coeruleus, it doesn't mean that critical lesion is just of the serotonin-- of the norepinephrine neurons. You get an amazing syndrome.

When it was first done by Gervais in France with cats, it was pretty early very clear what was going on, because the cat would go to sleep and then he would come to a REM period, as indicated by the electroencephalography recordings, and rather than just remember what usually happens in REM sleep, the animal becomes very relaxed, except for eye movements and some twitching and the extremities, the same thing people go through. But now, when they entered REM sleep, the cat got up and moved around, often showing fragments of fixed action patterns, like attack behavior, striking out imaginary objects.

And because that's part of the evidence that in that region there's a specific mechanism for removing descending influences on motor neurons, and if you get rid of it, then when the brain becomes active in REM sleep, you basically act out the dream. And it's very rare in neurology to have people with this, but there are one or two cases like this that I have read where they lose their REM atonia, rapid eye movement sleep stage, relaxation of the muscles. This is where the locus coerulus itself is in the textbook diagram, it's in the [INAUDIBLE] hindbrain below the cerebellum.

Also note that lesions in that region can completely abolish REM sleep, OK? But in fact, these lesions we're talking about will leave REM sleep, they just remove the atonia of REM sleep.

OK we'll mention a little bit about these other systems. There's many acetylcholine neurons in the reticular formation of the brainstem, and we know now that ascending influences from there come into the midbrain reticular formation and [? tween ?] brain, and cause an activation of the forebrain. I also mentioned the acetylcholine neurons in the basal forebrain, which are known to be very important in memory. How much that has to do with this activation, how much it has to do with things more specific to memory is not so clear.

Do some of you know what the disease is, where these acetylcholine neurons are begun to be lost, that's correlated the loss, is correlated with memory problems? Alzheimer's disease, that's right. There are many other changes in Alzheimer's disease too, but that's one of them that's been found to be pretty important in the debilit-- the cognitive losses in Alzheimer's.

I just want to mention here before we go on to studies of waking animals and habituation to novel stimuli that involve these same systems another type of neuromodulator that has been less studied, namely chemicals in the cerebrospinal fluid. The convincing experiments-- now they actually know what some of the chemicals are, although exactly how they're integrated with these other systems it's not so well known, but the initial discoveries involve very straightforward experiments they would have.

They would actually remove cerebrospinal fluid from a sleeping animal and inject it into the ventricular system of an animal that was awake. And of course, they did all the controls, so they would remove it, or remove fluid from a waking animal as well. And when they remove the fluid from a sleeping animal, it would cause the animal you injected it in to go to sleep, not if he was awake. So there was something different about the cerebrospinal fluid that influence the brain of the other animal.

All right. Now, I've given you another handout today. It's a good introduction to sensory systems. We'll be talking about, starting to talk about the visual system.

Before we do that, we're going to talk a little bit about novelty responses, orienting responses in habituation. They involve these axon systems with widespread connections that we talked very briefly about. They involve sympathetic activation, and we know that the posterior hypothalamus, that area that [? Noda, ?] when he lesioned, caused animals to sleep all the time, it's a major area, along with midbrain reticular formation for sympathetic arousal. So we're going to review what that is.

We'll define the orienting response, or it was called orienting reflex when many studies were done in Russia. And then we'll talk about the various components of that, compare it to lie detectors. I'll go through a specific study, a very famous study of habituation of the arousal response in sleeping cats. We'll talk about it, how those studies can be used to study brain damage and electrical stimulation of the brain. Many of the studies, especially in Russia, were done in awake humans, and that added some very interesting aspects to those studies and led to some specific models.

Remember, I mentioned that if you do a [? servoicillate, ?] the brain in front of the cut is asleep, which in large brained animals is most of the brain. But if you put an electrode into that core of the midbrain, the area that an anatomist color reticular formation, you can suddenly get an awake brain.

Now, if you don't have the [? servoicillate, ?] easily and you do that, you not only get an awake brain, you get an awake animal. But of course, the [? servoicillate ?] has no control over movement, so you don't-- it was just the electrical activity. Now you could use functional imaging and do something similar.

In fact, functional imaging shows that when the brain is awake, indications are that it's accompanied by consciousness, which means that a animal that-- or person that's completely comatose, according to his motor activity, might have an awake brain part of the time, and imaging studies have supported that and that people will show specific responses to their name, for example. You know, they answer to questions and so forth, even though they cannot make any other response.

There are different kinds of arousal, and you'll see that as we go through this talk. And these are topics that we'll cover now in the-- I think we said enough about this before. So as it comes up in the lecture, we'll review it. OK.

If you activate posterior hypothalamus or membrane reticular formation, you get activity of the sympathetic nervous system-- not parasympathetic, sympathetic nervous system, which, whenever it's activated, causes very widespread effects on the body. If you activate one part, you generally activate other parts as well.

That can be caused normally by stimulation of sensory-- visceral sensory auditory system. There's other sensory systems can also cause it, but these are often the ones, if it's very intense, also causes pain and negative reinforcement, that is the animal or a person doesn't like it.

And this is what we're talking about, these areas. When we were talking about midbrain before, we divided reticular areas into semantic and limbic. Anyplace marked there, when stimulated, will give you sympathetic arousal. The same thing happens if you move into these regions in front of the midbrain.

If you go from the limbic areas here and follow axonal pathways, you end up in hypothalamus. If you stimulate in these regions, you get activation arousal of the brain, the forebrain. Same thing for posterior hypothalamus, and you get sympathetic activation for all those regions.

The same thing is true for the reticular formation outside these limbic areas, and this is the region they call the ascending reticular activating system because when stimulated, arouses the brain.

So what is the difference? Difference is that the limbic system, when you stimulate it, is accompanied by positive or negative rewarding effects-- it's pleasurable or painful-- whereas the other parts of the reticular formation here, that is not true. Might be very mildly rewarding, but that's not characteristic of the stimulation.

And furthermore, when you stimulate out here, if you repeat the stimulation, you get habituation. But when you stimulate in the limbic areas, you don't get habituation. So there's two kinds of arousal mechanisms.

When you are exposed to something novel, novel sensory input, it causes transient sympathetic arousal, and it's that response that's called the orienting reflex by the Russians. In the West, it was often called the orienting response, or the arousal response, studied by Americans and Canadians the latter half of the last century.

To get it, you need a novel stimulus unless you're dealing with a stimulus that's associated with reward. In which case, you can get the arousal without the novelty. That's why when your name is called, you'll generally get an orienting reflex, including some sympathetic arousal, because your name is associated with positive or negative reward, hopefully positive.

Here's how we can define it. First of all, as I've mentioned, you get the EEG arousal, we call it. Remember, that's the flattening lower voltage, faster desynchronized activity. But you also get other things. You get a lowering of sensory thresholds. And every sensory modality, when you get that activation, you actually become more sensitive to stimuli, the various mechanisms for that, including some that act close to the periphery.

If the novelty is great enough, behavior will actually stop and you'll get an orienting movement. That is an animal can be doing something else. It can be engaged in feeding or foraging, or whatever, and he will just stop doing what he's doing and orient. Of course, that has obvious adaptive effects because he may have to deal with a predator or something else important for his life.

And you get sympathetic arousal. With sympathetic-- these are the science now of sympathetic arousal. We talked a little about that when we talked about the sympathetic nervous system in the first half of the term. Pupils dilate, you get increased muscle tone.

There are vascular changes too, and they're different in the limbs and head. In the limbs, like in the finger it's often measured in these studies, put a little cuff on the finger and the volume will decrease, and it can be very transient. It happens immediately with the novel stimulus. There's a constriction in the limbs. But in the head, you get vasodilation.

You also get electrical changes in the skin. It's called the galvanic skin response, and that's often used in the laboratory. You can also record heart rate and respiration, and you will see changes. For the heart, it's usually a normalization. So if the heart is beating more slowly, it will speed up. If it's beating very fast already, it will slow it down.

Those are the same measures, by the way-- and I just like to point this out since you read about this every once in a while, about lie detectors, all it is, they're measures of these things, sympathetic arousal. And I just want to point out here that in either case, you have a conflict.

With the lie detector, it's obvious it's conflict between what you know to be the truth and what you're actually saying, and that causes sympathetic arousal. And a normal person really can't inhibit that very well. I mean, maybe you can learn to do it. Some people can fool these machines, but it's very difficult for most people. It's certainly not a foolproof method to detect a lie, but that is what's involved in lie detection.

In the case of novel stimuli, the conflict is between what we expect based on our memory, and what's actually coming in. So it's another the kind of conflict. So in each case, there's some comparison being made that when there's a difference, it leads to the arousal response.

Now here is a classic study of the arousal response, was this. They were interested in habituation as a way of studying non-associative learning. The original study was done in back in the 50s. Here's what they had. They had cats with electrodes implanted in-- these were not microelectrodes, they were larger electrodes.

Similar, they got recording similar to the electroencephalogram, which are actually scalp potentials, induced in the scalp by underlying brain activity. They put the electrodes right on the cortical surface. The cat, as relatively-- it's much more difficult to get a good EEG from the cat, so they put the electorates on the cortex. They call the electrocardiogram.

And they did the study by waiting until the animal went to sleep. And then when the EEG indicated he was asleep, then they would present stimuli, and they were using pure tones. They could vary the frequency and intensity.

And I'll describe a typical session. They come in the lab, they hook the animal up, his electrodes to a recorder, and they wait for the animal to go to sleep. So these experiments lasted a long time. They were good electrophysiologists, and they were used to working all night. OK. So if they'd done it in the day, they might have found it'd have been easier to get the cat to go to sleep.

So they'd wait. Of course, there was light in the lab, which also may have complicated it a little bit. So what is the indication that the cat is going to sleep?

Well first of all, just behaviorally, the animal go to a certain position where he wants to sleep, and he'll curl up, always do preparatory movements, and lie down. Well, when he first does that, his electroencephalogram still shows the low voltage fast activity.

So they have to wait until the EEG indicates that the animal is sleeping. And first, you get little interruptions of the low voltage fast activity by what we call sleep spindles, little bursts of high voltage activity, somewhat slower, usually 12 per second or so, and then it goes back to the fast state [? sleep. ?] But then it starts shifting to the low voltage fast-- I don't have the tablet working here. OK. I would show you what that looks like, but you've probably seen recordings, the EEG recordings. OK.

So only when they had the animal showing this low voltage as high voltage slow activity for a certain period of time did they start presenting stimuli. And then they would suddenly present, for example, a 500 Hertz tone, and the animal typically would wake up the first time. He may not, but usually they had both a behavioral arousal and EEG arousal. OK.

So that was the response, and that continued for some minutes. For example, the first time they did for the one I was talking about, three minutes, the animal was awake, and then they got the low voltage fast activity again. Then they would repeat it, and they would get it over again. But the animal may not lift his head up that time at all, but they knew in fact, he had woken up, just from the EEG. And if you do that with people and you ask them about it later, it's very clear that they were awake, even though they may not have shown it.

So that's what they were doing. And they kept doing that and got less and less of a response, usually a shorter duration response, less of the behavior indicating waking up. And if they did that over a period of about an hour and a half with three presentations, eventually they got no response at all to that original 500 Hertz tone.

So when that happened, if they had enough time, they would then change the tone, OK? They could change-- this one, they changed to 100 Hertz, and they woke the animal, just woke up. Now, it wasn't a more intense tone. All it was is a different frequency. So that was the only novelty. That was enough to wake the animal up. And whether he showed behavioral waking or not, they got the arousal response.

Then they would get habituation to that. They would go back to the 500 Hertz tone, and they found out he maintained that habituation. So it's a kind of learning. He's remembering. Even though he's asleep, the brain is retaining the habituation.

And then if they change, say, instead of 100 Hertz, they went to a higher frequency tone like 1,000 Hertz, they could get an activation. The first time they did that, it was for three seconds, and then they could get habituation again, indicating that there was a frequency specificity. And in fact, the more they changed the frequency, the longer the arousal response they got.

These are the properties that in their summary of their work they recorded from various brand sites, and they got the same thing. It didn't matter whether they were over the occipital lobe or central cortex or temporal lobe, they were getting the same thing pretty much. It would be small differences, but in general, the results were very similar.

It was specific for frequency, and there was some generalization on the pitch continuum. So the more the change, the more the arousal. And that's what we call generalization.

They also noted that the change didn't have to be in frequency, it could be an intensity. They could make it louder. That's not too surprising. But in fact, if they made it softer, they could also get an arousal response. So it was specific to the loudness of the tone.

Even more interesting, if they just, instead of giving a one second tone, they gave, say, a three second tone, they could get an arousal response when the animal detected the change in timing. He would respond when it suddenly became longer than normal. So there was a lot of indications that it was the novelty the animal's responding to.

They also got pattern specific habituation. So they could get the cat-- and these were other studies, other nights they did this repeatedly in a number of different cats-- they would try using patterns. What's an auditory pattern? Well, it's something more like music.

So they would do, [WHISTLING UP]. So a lot of different frequencies, and they would keep doing that until they got habituation. Then they suddenly would change to [WHISTLING DOWN]. Same frequencies, same intensity, just a difference in pattern, and the animal would show the arousal response again. So it was pattern specific also.

They studied memory, noting that if they waited only a little while, the habituation was retained. But if they waited for hours, they got some recovery. If they did the same tone night after night, there was some habituation over days, but it was mainly at an increased speed of habituation. In other words, they get the arousal response again the next night. It was just, they got faster habituation.

They then went to using some of these cats to study brain lesions. For example, they tried deblating the auditory regions of the neocortex. They found that they could still get the frequency specific habituation, but they couldn't get that habituation to the tonal patterns anymore. And they couldn't get frequency modulated tones-- they couldn't get habituation specific to the kind of frequency modulation they were using.

They tried going into the midbrain and cutting the pathway from inferior colliculus to the medial geniculate body. So now that means auditory input, which comes in, and the hindbrain was reaching the midbrain, but it couldn't reach the former in anymore, that pathway comes into the medial geniculate body.

And if they did that, they could still get habituation to intense tones, but it generalized to all tones the same intensity, it was modality specific, such it's this ability to even in brain damaged animal to study this kind of learning that led people to begin to use methods like this, using these measures of sympathetic arousal to study sensory abilities in babies because, obviously, they can't talk, they're not going to tell you that they can hear. But you can look at their sympathetic arousal effects and find out if they can detect the novelty, indicating that they have sensory abilities.

After that-- sorry, these were based on that earlier study, and the date for the discovery of the ascending reticular activating system was 1949 in Italy. But much later, 12 years later, it was done in a much more specific studies of rats that was paralleled in many ways to the study, the behavioral studies in animals and then later in people.

They were stimulating the brain stem reticular formation. They would have electrodes in different parts of the midbrain reticular formation, for example, and they found again that they could get habituation with repeated stimulation at a given locus. They got recovery if they waited a certain period of time. They got, if they change the pulse frequency of the stimulation, they would get arousal, so that was similar to what they could get with behavior. If they change the locus from one part of the membrane to another, they would get the arousal response again. So it was specific to location.

They also found certain locations where they didn't get habituation at all, and I mentioned this already. These were the areas that were in the limbic system in the central gray or in the ventral tegmental area, if they were in the midbrain. And we know there they were stimulating areas which, behaviorally, appear to be rewarding or punishing to the animal. So they could get-- in other words, stimulating the reticular formation gave effects very parallel to what they were getting in the behavioral studies.

Let's go then to studies of human beings. And many of these were done by Sokolov, Eugene Sokolov in Moscow. He came and visited this Department at MIT after he had done many of these studies. He was very well known for them. I remember when he came, he spent most of his time using the big computer because they didn't have them in Moscow as he was working.

All the kind of same properties they found studying humans-- now, what they did, these were awake people sitting in a chair with measures of sympathetic arousal. And usually, they were using the volume of the finger and galvanic skin response. These were easy to measure. And when you give a stimulus, you get these transient effects on sympathetic arousal, transient sympathetic arousal.

All the same properties we were talking about, they discovered with humans. But then with humans, they could do some additional things. I mentioned this was true of cats too, they could decrease intensity and get an arousal response, but he also discovered you could just, in a train of stimuli, if you suddenly emitted a stimulus, that was novel, and that would lead to an arousal response. Changes in duration would lead to an arousal response-- changes in anything that the person detected as different. OK.

The work with humans led to a different kind of model than people were working on with animals. Let's talk about the simple model first, central adaptation. Gabriel [? Horne ?] in England and many others have done this, and it's been the most common model of habituation. It's the model used for spinal habituation, of spinal reflexes by Richard Thompson and others.

The model is central adaptation. I don't if they illustrate that here. Yeah, I do. OK. It's considered the most parsimonious model for habituation.

In general, we think of adaptation is different from habituation, because adaptation is peripheral. With adaptation, with repeated stimulus, you get less and less input. If it's your stimulating the skin, you have less input coming into the CNS. That's adaptation. It's a peripheral decrease with repeated stimulation.

But now, if you simply move that centrally, and say at a central location at a synapse in the central nervous system you're getting decreased sensitivity with repeated stimulation, then we call it habituation. [? Horne ?] said that when you get a change like that, it's self-generated depression. That's the term he used.

The problem is how can you account for habituation to decrease in intensity? Well, let's see. That's not very hard because you have neurons that are intensity specific, in the auditory system in particular, we know that. So some neurons respond best to one intensity, some neurons respond best to lower intensities or higher intensities. So as long as you have that kind of specific detection of stimuli, the self-generated depression or central adaptation can explain habituation effects.

What they don't explain easily is time dependent effects. In other words, you suddenly omit a stimulation, a stimulus. We don't know of neurons that are tuned to nothingness. So that's a big problem. And Sokolov, it led Sokolov to argue that you need a different kind of model to talk about that, a much more complex model.

So in his theory-- I'm just going to go over this briefly. It's related to something I mentioned in the introductory lectures-- he said the brain must have a model of the world, a model of the perceived world that it's comparing with inputs.

He assumed that the cortex and reticular activating system have very different roles. We know they each get sensory inputs. He claimed that in the cortex is where we form a model of the stimulus-- that's our memory-- compare it all the time with current input, and when there's a mismatch, you get activation of the reticular activating system.

I've sketched out the way he initially presented it, it's very simple. He has the inputs coming in to the reticular system and the midbrain, and as well as the neocortex. He's not showing the anatomical pathways involved. This is where he says there's a model of the stimulus, a memory is being compared with the input.

If there's a mismatch of the internal model with that input, then he claims there would be activation of the reticular system. When the reticular system is activated, it affects the cortex. So you get the EEG arousal, but you also get behavioral changes. General arousal effects, we associate with synthetic activation, and more specific effects of orienting movements.

And this is the way I said it, here's the reflex level, we have sensory analysis, compare to neurons in an output, the motor system. You have the model this-- of course, it should be much bigger-- a model of the sensory world, which is compared all the time. The comparison--

Am I going over my time? I don't have my watch today, I'm sorry. What time is it? I should have told somebody. Are we over? OK, so we'll finish this up next time. Sorry.