ABBY NOYCE: So going over quickly what we did on Tuesday. So we talked about the fact that this long-term-- hanging onto long-term information, long-term memory. Learning of new facts seems to depend on changes in how strong a synapse is. So we know that when you have two cells that are joined into the synapse, then if the first cell fires, then it releases a neurotransmitter that changes the likelihood of the second cell firing.

So you can think of a strong synapse, a strong excitatory synapse is one where if the first cell fires, the second cell is really likely to fire, whereas a weaker excitatory synapse would be one where if the first cell fires, the second cell is only a little bit more likely to fire than it was before.

And we talked in some detail about one mechanism that seems to underlie this, which is long-term potentiation, which happens at these excitatory glutamatergic synapses. Depends on two types of receptors, one which is the AMPA receptors, which are a sodium channel, an ionotropic sodium channel, and which will open and allow sodium in any time that glutamate is released into a synapse. And then these pickier NMDA receptors. That's backwards. I'm sorry. And NMDA receptors only open when the potential across the membrane at the synapse depolarizes to about minus 35 millivolts. So when there's a lot of sodium already coming in, then the NMDA receptors open up. And they also allow in as well as sodium, what other ion that causes long-term changes in the cell?

AUDIENCE: Calcium.

ABBY NOYCE: Calcium.

AUDIENCE: Calcium.

ABBY NOYCE: Calcium. Right. Remember, calcium acts as a second messenger, and it triggers the activity of all these other proteins. So summing up what we talked about with memory. So we know that when you experience something, then you get these patterns of cortical activity starting in your sensory areas, and moving outwards from there from primary sensory cortex to these association areas that do things like object recognition, or parse the language that you're hearing.

And so you can think of any given experience as being a particular pattern of neuron firing.

And we know from last week that this area in the prefrontal cortex is key for attending to experiences, to allowing one or another aspect of what we're experiencing to come to the surface, to be the thing that gets processed.

And so we can model what's happening in memory as allowing the prefrontal cortex, and to take all of these experience representations, and funnel them into this medial temporal area where the hippocampus is. And the hippocampus takes all of this input, and it strengthens the connections between them so that you can form a memory of an experience.

So the way we think this happens is that when you first form like an episodic memory, a memory of something that happens to you, then what happens is that synapse strings between the hippocampus and other parts of cortex get changed so that the hippocampus can bring up all the pieces of that memory at once so that you bring up that pattern of activity that you had when you actually had the experience. That episodic memory involves recreating, recapitulating this pattern of activity.

And so when you have one aspect of a memory cue other parts of it, the idea is that what's happening is that by activating the representation for this one part, that then brings out that hippocampal through the hippocampus then activates all of these other parts, and let's you get the whole memory. And over time, as you remember things either over time or through repeated retrieval of these memories, then the links between the cortical representations themselves become stronger. And you get this idea where memory is consolidated, where it moves away from depending on the hippocampus, and into just cortex.

If we look at our retrograde amnesic patients like HM, remember that his memory for distant past events, childhood events was really good. His memory for events a few years before his surgery was really bad. So there's a lot of evidence from other patients in similar situations that you need the hippocampus for recent episodic memories. You don't need it for older ones. Whoa, memory.

Does that make sense? This idea that at first, the hippocampus can bring up all of these different pieces of a representation, than over time, one of them can trigger all the others as the connections between the cortical representations get stronger? All right.

Moving along. Numbers. So we know that people can in general do math. Anyone here like math? Anyone think they're kind of good at it? Whoa. All right. Got probably a non-typical sample of the population here. So doing basic arithmetic types of math, which is, of course, not the only kind of math or even the most interesting kind of math, but it is, one, the kind of math that most people know about, and that most people encounter in their daily lives, and that most people are taught to do. So it's the one that's been most studied and the most tested.

Seems to require three things that most human beings can do. There's this innate sense of number. This sense of what numbers are little, what numbers are big. This ability for small collections of items to look at them and know, without counting, how many items are there.

And then there's this second step. It's this ability to, for example, count, to connect number names with numbers, with items. And thirdly, you need to have an ability to follow algorithms, to follow the steps in a process. Think about doing addition, and carrying numbers. Something we know how to do. Or even the basic if you're multiplying it by 10, you stick a 0 on the end. All of us probably learned these little tricks really early, and we know how to do them.

And this fact that the ability to follow algorithms is so important is you see a lot of students who can follow all the steps in the math they're doing, and can get the right answer, and don't really understand why they're doing this, or how it works. And you often see people who feel like it doesn't make any sense, because they don't have a good feel for what the underlying numbers they're working with are.

So let's talk first about this basic sense of number idea. I'm going to briefly show you about half a second, a little less, show you an image with some dots in it. I want you to tell me how many. Ready? How many?

AUDIENCE: One.

ABBY NOYCE: One. Was that easy?

AUDIENCE: Yes.

ABBY NOYCE: Want to do another one? How many?

AUDIENCE: [INAUDIBLE]

ABBY NOYCE: All right. Good. How many?

[INTERPOSING VOICES]

ABBY NOYCE: How many?

[INTERPOSING VOICES]

ABBY NOYCE: I hear fives. I hear six. How many people think it was five? Go ahead. Don't worry about being wrong. Raise your hand with what you actually thought it was. How many people think it was six? Sevens? What did you think?

AUDIENCE: I wasn't looking.

ABBY NOYCE: [LAUGHS]

AUDIENCE: I looked away.

ABBY NOYCE: So I noticed that our consensus went down. Was that one harder?

AUDIENCE: How many was it?

ABBY NOYCE: Six.

AUDIENCE: Yes! [LAUGHS]

ABBY NOYCE: Want another one? How many?

AUDIENCE: 11.

ABBY NOYCE: [LAUGHS] I don't think it was. I think it was more than that. 1, 2, 3, 4, 5, 6, 7-- I think it's 12.

AUDIENCE: Yes!

ABBY NOYCE: But notice that at this point, we have to count them.

AUDIENCE: Well, I was close.

ABBY NOYCE: You were close. You're estimating is good. So for numbers up to about three or four, depending on whose papers you're reading, people are fast and accurate. And they're equally fast. The difference it takes you to say, that was one, versus that was two, versus that was three, versus that was four, it's flat. It's the same amount of time for any of these responses. For larger numbers, people's estimate for doing it fast like this drops off. People can get pretty close, as you guys all demonstrated when we had six, and we had a couple of numbers on either side, or when we got that bigger number and I heard 11, and 13, and all right in there, around 12.

But for larger numbers, to get an accurate answer were slower. And we're not as accurate. And one thing that happens with larger numbers is that as a collection increases in size, the time it takes people to answer how many things are you showing me goes up linearly. For each extra item, there's a certain amount of processing time that's added. So what seems to be happening is that we're counting, is that there's some good behavioral evidence that for collections of items above about 4, that people have to do this extra bit of processing per each item that's shown.

So this ability to look at a screen very quickly and be like, there's three, there's two, there's four, is called subitizing. Cool word for you. S-U-B-I-T-I-Z-I-N-G. It's spelled like it's British, mostly because I think the people who do real math psychology work are mostly Brits, or they kind of started it. And there's one theory that says what's really happening in subitizing is that we're looking at shape. So one dot, pretty easy to spot, right? Don't need to count it. It's just one dot.

Two dots, no matter how you arrange them, are always going to form a straight line. Three dots, unless you have the totally unlikely thing of lining them all up in a straight line are going to form triangles. No matter what. Four dots randomly arranged are going to form some kind of quadrilateral. Now, notice that as we go up, there are other possibilities. You could do three dots in a straight line. You could do four dots as a triangle with a dot in the middle, or as a straight line.

And four, again, is where you start seeing people's performance get a little bit sloppier, but still in the subitizing quick range, and not so much in the linear addition of time counting range. So one thing that says what's going on here is really shape analysis, and other folks who say, no, no, no, it's an intrinsic number sense. But either way, this is a distinction that we are really good at.

What about other kinds of critters? So we know that humans are good with numbers. We like to think that humans are special. Humans are not always as special as we think we are. Numbers is one of the place where you can't do it. Otto Kohler was working in the '40s and '50s. German guy, as you might have guessed. And he trained birds to distinguish between numbers in the two to six range using dots, collections of dots.

He was working with ravens. And he would show them a card with between two and six dots arranged on it. And then there were two food receptacles with different numbers of dots covering the food receptacles. And the one that matched the number of dots that the bird was originally shown, not in the same pattern, just the same number of dots, was the one that had food in it. And these birds could learn to do that kind of comparison between this group of dots and that group of dots.

Alex, the noted gray parrot who died last fall, maybe? Recently, anyway. It was all over the news. So a lot of people have always thought that parrots are just mimicking. Parrots who say words are just mimicking. Irene Pepperberg believed strongly that this is not true, that parrots can at least learn some basic concepts. And she taught Alex to distinguish some colors, shapes, and numbers up to five.

So Alex, probably for this tray, could not say how many things there were. But for a small group of items, you could say, how many are there? And he would say, two, or four, or three. Definitely, again, with reasonable accuracy, could distinguish between these different groups of numbers. This probably doesn't necessarily mean that either of these birds are counting, per se, in the sense where we think of it where you're going one, two, three, four. But just like we have an intuitive grasp of the sizes of different amounts of things, different numbers of things, these critters can do the same thing.

One course that did not do arithmetic, you guys may have heard of Clever Hans. So this is way back right around the turn of the 20th century. Wilhelm von Osten claimed that he had taught arithmetic to his horse. And they toured the country. They toured the continent. They drew admiring crowds. He would say, Hans, what is 2 plus 2? And Hans would sit there and tap his front foot.

[TAPPING FOOT]

Four times. It was pretty convincing. He could handle fractions. He could handle addition, subtraction, multiplication.

AUDIENCE: How would you demonstrate a fraction?

What's 1/3 plus 1/3? [TAPPING FOOT]

As two pieces with a pause in the middle.

AUDIENCE: How would they know [INAUDIBLE]

ABBY NOYCE: How would they know the horse was doing it? The horse is the one doing the tapping. The horse would tap his hoof.

AUDIENCE: I thought there was another guy sitting there.

ABBY NOYCE: No.

AUDIENCE: I saw a cartoon with that once. I think that's *The Wild Thornberrys.* They had the horse, except there was somebody backstage kicking the horse.

ABBY NOYCE: I saw that episode. Yes.

AUDIENCE: I saw that.

ABBY NOYCE: This was a little subtler than that. So in 1904, a committee of psychological experts investigated this, observed, decided that there was no trickery involved. Nobody was poking the horse from backstage or anything like that. And concluded that it was for real. And a guy named Oskar Pfungst. And I don't think I can pronounce that right, but I'm going to try. Pfungst. In 1907. He didn't really buy this. He'd been part of that original study committee, and the committee had come to the consensus that it was real. And he was just like, yeah, I can still see some issues here.

And he tested Hans in a variety of situations. He had situations where somebody other than von Osten was asking the questions. He had somebody other than von Osten ask the questions when von Osten was not in the room. He had somebody state a question in von Osten's hearing, and then write it on a board which was oriented so von Osten couldn't see it, but Hans could, so that Hans was seeing the question other than the one that had originally been proposed.

And the conclusion that he came to was that whenever the trainer did not know what the question was, Hans was wrong. When the trainer knew what the question was, Hans was right. So the conclusion that these guys came to is that consciously or unconsciously, von Osten was cueing Hans in some way, cueing him when to stop tapping, more or less, to tap until he relaxed and it was the right answer. The general consensus seems to be that the trainer would get tensor, and tensor, and tensor as the horse approached the right number of taps, and when he got to the right one would relax, and the horse could pick up on this cue, which was probably a very subtle cue, and figure out that the right thing to do at that point was to stop tapping, which is very clever, but it is not arithmetic.

This kind of cueing is one of the reasons for things like very careful double blind clinical studies, the fact that when one of the people in the room knows what's going on, no matter how careful they think they're being, other people can often pick up on what that person knows. And it's one reason.

So Clever Hans, one of the things that this incident did is it made a lot of psychologists very dubious about any and all claims of animal arithmetic abilities. So those number abilities tests that we started seeing in the '40s and '50s, everyone was really skeptical for a while until the results started being really solid.

AUDIENCE: Was this actually proved?

ABBY NOYCE: Was what actually proved?

AUDIENCE: That we was cueing by getting tensor. Because he could've been blinking like one, two, [INAUDIBLE]

ABBY NOYCE: Yeah. So from what I've read about this, the general consensus seems to have been that von Osten thought it was for real. von Osten seems to have at least convinced people that he was not deliberately cueing the horse. He really thought Hans could do this, that it was not deliberate.

So there could have been other cueing things that Hans was picking up on. Pfungst, the guy who finally disproved it did something similar with human subjects, where he'd have somebody show them a arithmetic problem, and he would answer by tapping. And he said, he could pull enough cues off of random people to know when to stop tapping about 80% of the time-ish. And he said he described it as this growing tension in the person who is listening.

It's 1907. It's not quite up to modern research standards. Horses don't go into laboratories very well. But nonetheless, it's an interesting story. It's an interesting case of where there was a confound that slipped right past people the first time they looked at it. Remember, a confound is something else that's varying along with what you're trying to study that can mess up your results. So Hans is clever.

So we know this idea that humans started developing number sense. When did they do it?

Well, so Jean Piaget is the classic developmental guy. In the '50s, he set up this set of stages, developmental stages. So at this age, children will do this. And at that age, children will do that. And one of the things he pointed out, he claimed was that four and five-year-olds, if you take a bunch of items, say, six items twice, and we line them up in rows, and say, which row has more items? The kids will say, they're the same.

And if the experimenter then, with a kid watching them, takes one of the rows and spreads them out-- and I'm going to make my things wider, which isn't really what I want to do. Spread out. And says, now which one has more rows? The kid will say, the longer one. So Piaget pointed this out. And Piaget says that this means that kids who are under about five don't have this core idea of numerosity where unless you add or remove something to the set, the number stays the same.

Some people have been kind of skeptical of this. One reason for being skeptical of it is if you do this with two-year-olds, they get it right. Three-year-Olds get it right. Four and five-year-olds get it wrong. So one hypothesis is that human children lose number ability between the ages of four and six. That seems unlikely.

Other people have pointed out that around age five is when kids start really thinking about this idea that other people have motivations and beliefs that underlie what they're doing. They start being able to reason about why other people are doing and saying things in a way that's more sophisticated than younger kids can. And that logic says that-- so I just told this grown up, who is clearly smarter and more clueful than me, that they're the same. And she moved them, and they're clearly still the same. Why is she asking you this question again?

She must mean something other than what she just asked. I must have misunderstood the question she is asking. She must really be asking about the size of the row. And will then trying to give the right answer, trying to make the adult happy will pointing to the longer row.

AUDIENCE: [INAUDIBLE]

ABBY NOYCE: Somebody. So we said the two and three-year-olds who are too young to do that kind of complicated reasoning about the motivations behind other people's behavior will get this right. Four and five-year-olds, that age where if you are doing this by asking them questions-- has anyone here ever tried to have a conversation with a four or five-year-old? It's a little weird, isn't it?

So one of the problems with Piaget's original experiment is that it depends on having a verbal conversation with a four or five-year-old, which we know that little kids, and little kids and language can be a little wonky at times. So somebody else said, what happens if we give them M&Ms, and we show them two rows of M&Ms, and one of them has four M&Ms, and one of them has six M&Ms? And instead of saying, which one has more, we say, you can pick one row of M&Ms and eat them.

This gets around the language problem. This gives the kids a nice, strong incentive to pick the one that has more. And when you frame this problem in this way, four and five-year-olds, the kids who Piaget says don't understand this core concept of number, that number is unrelated to the amount of space things take up, get it right every time. So this is another piece of evidence for that other hypothesis that these kids are figuring that they misunderstood the question, and trying to parse it in some way that makes more sense.

So we know that toddlers have this kind of core sense of number of what's more, what's last. Two-year-olds can't count, by the way, but they can do this intuitive judgment. What about littler kids, once we start getting really down into baby size? So this guy named Starkey did a bunch of experiments with babies between 16 and 30 weeks of age. So that's between four and eight months.

And when you want to work with babies, with kids who are too young to talk, too young to have a whole lot of hand-eye coordination, you start having to get clever experiment designs in order to figure out what they're doing. So Starkey said, aha. We know that babies are interested in things that are new and different. And that if I give them they've seen a lot of times and something that is new, they will spend more time looking at the thing that is new than the thing they've seen before.

So they had kids sit on their parents' lap, and they videotaped them so they could confirm where their eyes were looking. You probably can't use eye trackers on babies. I think they move around too much. But this was in the '80s before they had good eye-tracking software. And they had the babies look at a screen. And they'd show a picture of two dots, and the babies would look at it for a little while, and get bored, and start looking around the room. And they'd show a different picture of two dots, two dots in a different arrangement. And the kids would look at it a while and they'd get bored faster.

And you show them two dots a few more times, and they get bored faster and faster each time. Their attention starts wandering. If you then change it up to a picture of three dots, the kids look at it again for a long time, like they did the first time they saw two dots. Once, it's random. But if you do it across, say, 20, 30 babies across several trials, it starts really seeming like the kids are understanding that there is a difference between two of something and three of something.

AUDIENCE: Is there a way to differentiate between the kids just sensing that there's a different picture on there, but not really understanding the quantity?

ABBY NOYCE: Well, remember that they're showing them several different two dot slides. So two dots arranged in different ways. So they're not responding to just the change. They seem to be responding actually to the change in quantity. They're probably not counting, but they seem to have this recognition that what's being shown is different from what was shown before. It captures their attention again. Somebody did something similar with younger infants, like under a week-old babies. And with kids that age, you can't even sit them up and watch them look at things. They just kind of flop.

[LAUGHTER]

You know what I mean? Like really, really, newborns are like, "deh." They just don't have any motor control at all. But what they can do is suck on stuff. Little kids, newborns. It's one of the things that babies can do right away. And what researchers have done when they want to work with really young babies, these newborn babies, is set something up where the kid has a little bottle nipple to suck on, and it's wired up to something that controls what's being displayed to the baby in some way.

And newborns don't have good visual perception yet. They can't focus their eyes on anything very far away. You guys probably know this. That's why everyone always has the mobiles in the crib for the baby to practice focusing on and looking at.

AUDIENCE: [INAUDIBLE]

ABBY NOYCE: Or with the black and white patterns, the high-contrast patterns.

AUDIENCE: I thought it was to make parents feel better.

ABBY NOYCE: [LAUGHS] Many child-raising things are to make parents feel better. I will totally grant that. Anyway, so they had these little kids, these newborns. And they had one of these nipple setups so that when they sucked on it, it would play a nonsense syllable. And so they would do, again, the two versus three thing. They'd have it play a two-syllable nonsense word every time the babies sucked on it. And the babies would eventually be like, hey, look, I can make noises happen, and suck on it a lot. And eventually, the rate would slow down.

And if they changed it to three-syllable nonsense words, the babies would, again, respond to the change by acting more interested. In this case, sucking on the nipple again to get these new words, these new sounds that were different from what was just being played to be played at a higher rate. So that's some evidence, at least, that very, very young children can make this distinction between two different small numbers.

Numbers seems to be one of these things that's intuitive. Not counting numbers, not arithmetic numbers, per se, but this intuitive grasp of small numbers and the differences between them seems to be one of these really deeply-ingrained human capabilities, and not just humans, for other animals, too. But it's cooler in humans, or something.

Anyway, the other thing that Starkey show that was really cool is that not only could babies make this distinction between two dots and three dots. There's some evidence showing that babies seem to make the connection between a display of two items or three items, and the soundtrack of two beats or three beats.

And this was, again, with older infants, 48-month-old kids. And again, the sitting on mom's lap. And they had two screens for them to look at, one which showed two items, I believe, actually, like two apples, or two balls, or something, and one showed three. And they would play a soundtrack of two or three drumbeats.

And what they discovered is that the babies would spend more time looking at the screen that had the same number of items as the drumbeats, which Starkey takes as evidence showing that the kids are able to make this connection that both of these things are two in some abstract way, even though they're coming in in different modalities. One of these is visual and one of them is auditory. Babies, they're smarter than you think.

AUDIENCE: My parents say that on the day that my brother switched from mother to the bottle, he was listening to the Handel's *Messiah.*

AUDIENCE: The what?

AUDIENCE: Handel's *Messiah.* You've never heard of it? It's the [INAUDIBLE]

ABBY NOYCE: Not everybody is classical music people. That's OK.

AUDIENCE: They like to tell a funny story. They say that my mom had to go out, so dad was stuck with the job of feeding my older brother. And then for the first part of the night, he'd refuse the milk bottle. And he actually used his tongue to push it out of his mouth. But then when they got to the part of the "Hallelujah Chorus," he'd calm down.

ABBY NOYCE: Cute. All right.

AUDIENCE: [INAUDIBLE]

ABBY NOYCE: Moving right along. So we have this innate number sense of smallish numbers. The lack of having this is called dyscalculia, kind of equivalent to dyslexia, difficulty reading. Dyscalculia, inability to work with numbers. These are some cases by, oh, shoot, Brian-- something that starts with B-- who is at Cambridge in England, and has been working on this for a long time. Like I said, the Brits did a lot of this work in the last couple of decades really putting it together.

And he started collecting interesting patients. So [INAUDIBLE] had an operation to remove a tumor in her left parietal lobe. And after that, her general intelligence remained more or less intact. She scored well within the normal range on most IQ tests. Her linguistic ability remained intact. She could talk to the examiners. She could answer all sorts of logical questions about her world.

But she didn't have this sense of numbers anymore. She couldn't do that that's one thing, that's two things, that's three things, that subitizing, that instant recognition task that we can do. She couldn't do arithmetic, other than the fast facts that she'd managed to retain. So she could still recite off her multiplication tables, but it didn't make mean anything to her.

And they tried to make the connection between the written numerals and this string of words that she knew. And it just didn't click. She couldn't make this comparison between 1 times 1 is 1, and 1 times 2 is 2, with the written-out version of it, or the fact that it meant anything. It was just a string of words that she remembered.

So some of the cases that you'll see with this are stroke victims, Alzheimer's victims, people who've had a tumor removed, people who've had some kind of damage to the left parietal lobe. There's also a few cases, they're much rarer, of people who are actually born without this sense of number. Again, this guy talks about a guy named Charles who can count, do simple arithmetic slowly on his fingers, like single digit addition and subtraction, uses a calculator for everything.

If you show him, for example, 7 and 4, and say, which one is bigger? He can say, one, two, three, four. I get to four first. Seven must be bigger. For numbers that are outside of finger-counting range, he can't do it. So these are rare inabilities, but this does seem to happen that some people just-- this innate sense that most of us have, it's just not there for these people. And the extent to which people can work around this is pretty impressive to me. I'm one of those innately fast at math people, and I can't imagine not being able to do this. But definitely impressive.

Counting. So this is moving from this innate, unnamed groups of number sense to this more precise sense of math, in which we're used to thinking about numbers. So counting let's you determine how many things are in a collection. How many chairs are in the first row? 1, 2, 3, 4, 5, 6, and then one up front here.

Really little kids have a hard time with this idea. You say, how many blocks are on the table? They'll say, five. You say, can you count the blocks? And they'll say, 1, 2, 3, 4, 5, 6, 7, 8, 9. And you'll say, OK, so how many blocks are on the table? They'll say, five.

The number that you get up to when you're counting the collection and the number of items that are in the set are equivalent doesn't click for, again, two and three-year-old kids. Or they'll count something twice. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15.

So counting is a learned skill. Little kids don't do it well. Bigger kids do do it well. Some cultures, even nowadays, have number words that go something like 1, 2, a lot, or 1, 2, 3, a lot, and really don't have counting in any kind of useful way any way that we would think of as counting. Presumably, a couple thousand years ago, there were a lot more cultures without these kind of intrinsic counting words.

You can still hear this. If you look at languages, you'll probably notice that the numbers for 1, and 2, and 3 behave differently than the numbers for later words. For example, in English, for numbers above four, how do you get the ordinal for that? Fourth, fifth, sixth. You just add that "th" right on to the end, and it goes right on up. But for the first three numbers, it's different. First, second, third. And you'll see this pattern in a lot of languages. You'll see it in French. Primer, seconder. And then it goes up with the "em" endings. I don't know any other number words that well. I used to.

But anyway, you'll see this thing where the first three numbers are treated differently in the language. You'll see this pattern is taken as reasoning that these numbers are treated differently in the brain, or that they're older than the other numbers. So counting doesn't seem to be an innate human ability the way that that low-level number recognition is. Working with these higher level numbers, these more precise ways of thinking about numbers is different. Thinking about more precise levels of numbers. We're going to do the dots again, but I'm going to show you two numbers. One on the left, one on the right.

AUDIENCE: What do you mean by bigger?

ABBY NOYCE: Larger in quantity. If the numbers are 11 and four, 11 is bigger. They're printed in the same size font. Which reminds me of an interesting experiment that I'll tell you about after we do this. So this is going to be like the dots. One on the left, one on the right. I want you to raise your left hand or your right hand depending on which one is bigger.

AUDIENCE: [INAUDIBLE]

ABBY NOYCE: And I you to do it as fast as you can. It's the one that's on the same side as the number that's bigger. You can handle that.

AUDIENCE: [INAUDIBLE]

ABBY NOYCE: So if the one on the left is bigger, you raise your left hand. If the one on the right is bigger, you raise your right hand. And try and be fast. Ready? And I'm going to, again, show them pretty quickly.

AUDIENCE: [LAUGHTER]

ABBY NOYCE: All right. Want to do another one? All right. All right. [LAUGHS]

AUDIENCE: Ow.

ABBY NOYCE: You OK?

AUDIENCE: That was my elbow.

ABBY NOYCE: All right. Was the last one harder than the other ones?

AUDIENCE: No.

ABBY NOYCE: No? So I think this is one of the things where if you do a bunch of them, they get harder. One thing that you'll see in general is that as people do this, this seems to be harder than you might think, that often, once you get into the rhythm of it, you'll see response times of up to half a second to decide which one is bigger, which one is not.

It also tends to be that for two numbers that are close together, people are slower and less accurate than for two numbers that are far apart. If the numbers are 1 and 25, people are very fast and very accurate. If the numbers are 24 and 25, people are slower and they mess up more. So one of the ideas underlying this is that we have this number line representation of numbers. We all remember learning number lines in school, right?

And one of the things that happens is that when we're doing a task like this, we're conceiving numbers as being on this mental number line, so that numbers that are close together, it's hard to judge which one's which. Numbers that are far apart, it's easier. And this is not so much in the consciously doing it sense, but this is a model for explaining what kinds of mistakes people tend to make in this task.

Other ways in which this mental number line idea seems to kick in is that people's mental number line seems to compress as it gets to bigger numbers. So if you think of it as the numbers from one to 10 are nicely spaced out and really far apart, the numbers from 80 to 90 are closer together. They don't seem as different. 82 and 85 don't seem as different as two and five do to a lot of people.

AUDIENCE: [INAUDIBLE]

ABBY NOYCE: Somebody did, which is the thing that Zechariah reminded me of. Somebody did something that's equivalent of a Stroop task. Remember, the Stroop task was saying the color of the ink, rather than the name of the color that was written. That was kind of tricky, kind of hard. Somebody did something equivalent where they'd show two numbers, one of which is a-- break the chalk-- is a three, and one of which is an eight, and say, which number is written in the bigger type? Don't tell me which number is the bigger number. Tell me which one is written in the bigger type.

And just like with the Stroop tasks, people seem to have a hard time inhibiting that automatic processing of number as number, and thinking just about the typeface. They're a lot slower on it than they are in the number as number task, whereas if the three was little and the eight was big, people would be really fast at it. The number size, and the type size line up. So we know numbers. We're good with numbers. We have a lot of information about numbers stuffed into our brains.

Let's talk for a minute about these representations of numbers. We all deal with numbers primarily as numerals. We've got words for them as well. And one of the things about numerals versus older writing systems, like Roman numerals, one of the things about Arabic numbers is that it lets you take advantage of your linguistic skills, your ability to learn a set of steps and use that to do things to these numbers. Multiply by 10 is add a 0, whereas in Roman numerals, you've got to switch everything over into different characters.

So it's a different kind of processing when you're manipulating numbers. You can build these simple algorithms for steps for adding or multiplying that we all learned in like third grade, right? And unlike older number systems, you didn't have to do the calculation and then rewrite it all. It was just right there. So numerals are important. They're one of the big things that made arithmetic at least be accessible to the masses, higher level arithmetic.

And they're, in some ways, simply a way of writing down number names. We all know that if I say 1,245, then you write it as 1, 2, 4, or 5. It's just a way of writing down the set of words. It's a shorthand. But on the other hand, numerals seem to be handled differently from the parts of the brain that handle language processing. And one example is a patient who had fairly early onset Alzheimer's who could read words, and who could read the written out names of numbers, even multi-digit numbers, was 50% accurate reading off a single-numeral names. Could read a one, or a two, or a three about half of the time. And not at all accurate at reading multi-digit numeral representations of numbers.

So would be able to read 1,245. Would not be able to read this representation of the same number. So that's one piece of evidence that the word representation of this and the numeral representation are being handled by, in some ways, different processes in the brain. One of them is intact, one of them is not. And there's evidence of the opposite case, too. There's a woman who had surgery on her frontal lobes, again, a tumor removal surgery, and lost most of her linguistic ability. She can speak, but she can't read, can't write, can't deal with written language, can still deal with numerals, and can still do arithmetic, as long as it just has just the numerals lined up on top of each other.

So if you think of it as 1, 2, 4, 5, plus-- she could do that. 4 is 13. 1 and 2 is-- that kind of arithmetic, she could still do, even though she couldn't read or write words at all. So that's what's called a double dissociation. You found a patient who has ability A, and not ability B, and another patient who has ability B, and not ability A.

And so in the cognitive neuroscience world, a double dissociation like that is the gold standard for saying that these two abilities are independent in the brain. That ability A doesn't depend on ability B, and ability B doesn't depend on ability A. That they're handled by separate processing modules.

AUDIENCE: Synapse.

ABBY NOYCE: Quick review of [INAUDIBLE]. Yes, it is a synapse. Excellent! What kind of synapse is it if we're talking about long-term potentiation? What neurotransmitter is going to be here? The main excitatory transmitter in the brain. So it's going to be glutamate.

AUDIENCE: [INAUDIBLE]

ABBY NOYCE: So we know since we harped on it for the first week of class, when an action potential comes down the axon terminal, it causes neurotransmitter to be released into the gap between them into the synapse. And it triggers receptors on the postsynaptic cell. For glutamate, there's two kinds of receptors that we care about. One of them is called the AMPA receptor. [INAUDIBLE] the NMDA receptor. N-methyl-D-aspartate something.

And the AMPA receptors aren't picky. So an AMPA receptor, when the glutamate binds to it, it opens. And AMPA receptors are sodium channels. That's a plus, not a t. So when glutamate is released into the synapse, AMPA receptors open, sodium comes in. This is good. So this is excitatory. It's a positive ion coming into the--

AUDIENCE: Don't you call them glutaminergic?

ABBY NOYCE: Glutamatergic, yes. So a glutamate synapse. Kind of like cholinergic, or dopaminergic. So sodium comes in. So this is an excitatory synapse. It's a positive ion coming into the cell. It's going to make the membrane of this cell less polarized. NMDA receptors are pickier because in their normal state, they've got this magnesium ion hanging out, blocking that channel. Magnesium ion is attracted to the membrane potential, that because this cell is more negative inside than outside, this magnesium ion is stuck into that channel there.

So even after the glutamate binds to this NMDA receptor, this magnesium ion stays put, unless this cell fires so many times that the membrane here depolarizers all the way to about minus 35 millivolts. So remember that resting potential is minus 70. So we're going to about minus 35 millivolts. And at that point, the electrostatic pressure on this magnesium ion decreases because this cell is no longer negative enough inside to hang on to it. Magnesium ion pops off, floats away out into the extracellular space, and then both sodium-- that's a plus, not a t. I Keep having this problem.

And calcium both can go through the NMDA channels. NMDA are channels for both sodium, which is excitatory, and calcium. And calcium does cool stuff. Calcium acts as a second messenger. Goes inside the cell, and changes a bunch of things about the cell's behavior. So one of the things calcium does is it activates a bunch of enzymes called protein kinases.

Kinases are enzymes that phosphorylate other proteins. They reach out, they grab a phosphate group, and a protein, and they glom, stick them together. In these cases, there's a bunch of different kinases. There's protein kinase A, protein kinase C, and one called calcium calmodulin kinase. So calcium is activating all of these. And this calcium calmodulin kinase, CaMK, has some direct effects on the behavior of receptors at this cell.

First of all, the calcium calmodulin kinase, the CaMK, remember, these phosphorylate things. It goes up. It will go to these AMPA receptors. It sticks a phosphate group onto them. And by changing the molecular structure of the receptor, it causes it, when glutamate binds to it and it opens, when sodium can flow in, it causes it to stay open longer.

So every time these AMPA receptors open up after they've been phosphorylated, more sodium gets in. So each AMPA receptor has a bigger excitatory effect than it did before that phosphorylation happens. Who's lost? Questions? Things that you would like to have repeated?

AUDIENCE: I heard something that [INAUDIBLE].

ABBY NOYCE: That's true. It's probably not directly correlated to this. It probably has more to do with the extent that epinephrine and norepinephrine affect your attentional systems so that you're focusing lots of processing resources on whatever is coming in so that things that occurred when you're having some kind of strong emotional response to something, for example, tend to be recalled very vividly. How old are you guys on 9/11? Middle school? Elementary school? That was a while ago. Yeah, see, OK.

I was a senior in high school. And I know exactly where I was, and how I found out that this thing had happened, and boom. It's this very vivid memory, because it was very emotional, very, oh my gosh, what's going on, the world is coming to an end kind of day.

AUDIENCE: [INAUDIBLE]

ABBY NOYCE: 2001. Yeah. So you guys are probably young enough that this didn't happen. But I know that for like me and my immediate peer group, this was one of these really defining moments of our adolescence. That bam, this thing happened and the world changed.

AUDIENCE: [INAUDIBLE]

ABBY NOYCE: [LAUGHS] It was September.

AUDIENCE: [INAUDIBLE]

ABBY NOYCE: OK, anyway. So calcium calmodulin kinase.

AUDIENCE: [INAUDIBLE]

ABBY NOYCE: Back to the chemistry! Calcium calmodulin kinase phosphorylates these AMPA receptors. Also, there might be other AMPA receptors hanging out in the spine of the dendrite further up that aren't on the membrane yet. And CaMK basically goes and gets these, and brings them up to the synaptic cleft. So it encourages these receptors that were not previously on the membrane to move to the membrane, so that there are more receptors on the membrane, which makes this synapse then more sensitive to glutamate.

Of the glutamate that's released into the synapse, more of it will bind to receptors. It will have a bigger effect, even without changing the amount of glutamate that's released. The other thing that all of these kinases will do, all three, is they'll find this protein called CREB, which is-- oh, shoot. I knew it on Tuesday.

AUDIENCE: Can you just put CREB?

ABBY NOYCE: You can just put CREB, yes. And CREB binds to specific regions on the DNA and affects the transcription of those genes. So it causes those particular proteins that are being coded for by those regions of DNA. It changes how they are expressed, whether more of them are synthesized or fewer of them are synthesized, which is why you'll see people saying that LTP, long-term potentiation, has a short stage, which is this stuff with the AMPA receptors being phosphorylated and more AMPA receptors being moved to the tip, and then a longer stage that has to do with gene expression and protein synthesis, which takes a few hours to really kick in.

AUDIENCE: [INAUDIBLE]

ABBY NOYCE: AMPA receptors and NMDA receptors are both glutamatergic receptors. They both respond to glutamate.

AUDIENCE: [INAUDIBLE]

ABBY NOYCE: Yeah, AMPA.

AUDIENCE: OK.

ABBY NOYCE: And AMPA receptors are just your classic ionotropic receptor. The neurotransmitter binds to them, they open up. A particular kind of ion gets to go through their channel. NMDA receptors are special because even after the neurotransmitter binds to them, they've still got that magnesium ion blocking them until the cell depolarizes past a certain point, so only when lots of AMPA receptors have already opened up, or the AMPA receptors have already been opened a bunch of times to let all that sodium in. So NMDA receptors are picky. They only open up when there's been lots of activity coming to the cell. Does that make sense?

So remember, this is instantiating this idea of neurons that fire together wire together. So when the presynaptic neuron is firing to the postsynaptic neuron, and the postsynaptic neuron is really depolarized, which means that it in turn is probably firing, then that synapse gets strengthened.

But if the presynaptic neuron is firing and the postsynaptic neuron only depolarizes a little bit, then it won't strengthen. It depends on when both neurons in the chain are firing is where you'll see this strengthening of the synapse, making it more receptive to that glutamate, so that when the glutamate is released, then it has a bigger effect on the postsynaptic neuron by putting out more receptors, by strengthening these receptors, by phosphorylating them. That's what that CaM kinase is doing, so that they stay open longer, so more sodium gets in. All of these are changes that are allowing that postsynaptic cell to be more sensitive, really, to the presynaptic cell. Are we good?