

NATIONAL INSTITUTES OF MENTAL HEALTH

ANNUAL AUTISM AWARENESS LECTURE

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The lecture convened at the National Institutes of Health, Mark O. Hatfield Clinical Research Center, Lipsett Amphitheater, Bethesda, Maryland, Kevin Pelphrey, Ph.D., Professor of Psychology; Director, Child Neuroscience Lab; and Harris Professor, Child Study Center, Yale University School of Medicine, speaking.

PROCEEDINGS:

Dr. Thomas Insel: Well, good afternoon, everyone, and welcome to the Annual Autism Awareness Lecture, which happens every April as part of Autism Awareness Month. This particular lecture is being brought to you by NIH and the Office of Autism -- or NIMH, I should say, and the autism -- the Office of Autism Research Coordination, or OARC, which Susan Daniels, who's here, runs. And along with many other things that they do, this lecture is one of the annual events that we look forward to.

This year we're particularly delighted to have an outstanding scientist who's going to take us through his particular story, both personal and professional, related to autism. Kevin Pelphrey, born in Kentucky, part of a military family, raised in North Carolina. Ultimately went to UNC to get his Ph.D. in cognitive -- in developmental psychology, and then went on and got a cognitive neuroscience post-doc at Duke, where he finally began to bring together these two interests, both

in modern cognitive neuroscience, especially social neuroscience, and an opportunity to think very carefully about development and how the developing brain begins to process social information. His work has been a model for many people in how to use neuroimaging in cognition together to understand social information processing. And you'll hear much more about that in just a few minutes from him.

He's currently the director of the Yale Center for Translational Developmental Neuroscience, which I think captures just about everything that he would want to say he's interested in. He's received numerous awards, most of the time while he's been at Yale, where he's also been the Harris Professor in the Child Study Center and a professor of psychology at the Yale School of Medicine.

His awards include a Career Scientist Award from NIH, the John Merck Scholars Award, and the APA's Boyd McCandless Award for Distinguished Early Career Theoretical Contributions to Developmental Psychology. He is supported by NIH, including a large center grant from NIMH, focusing particularly on girls and women on the spectrum. Also supported

by the Simons Foundation, Autism Speaks, and the NSF.

And on a personal level, I have to say that Kevin has been just one of the great people in this very exciting field of autism research, who's been able to talk about this not only from the standpoint of where is the science taking us, but how do we make that science useful. And he cares about that specifically because he's not only a great scientist, but a very committed father to a daughter who's on the spectrum. And that is, I hope, the story that we'll let him tell us about this afternoon.

Kevin, welcome, and thanks so much for being here.

[Applause.]

Dr. Kevin Pelphrey: Okay. Can everyone hear me? So thank you so much for inviting me. This is the first time I've really given a talk that's not focused just on science and the data. I am extremely nervous for the first time doing a talk in many, many years because this is really going out on a limb for me, but hopefully it won't show

very much. And, again, I'm honored to be here. This is really terrific.

So this is Francis, and Francis was actually born the day I first met Tom Insel. I don't think he knows this story, but the story was he was visiting for our Start Center. I was working with Joe Piven as a post-doc then at the University of North Carolina, and he visited. And I had been given the opportunity to present for three minutes, and many of my colleagues were given the opportunity to present. I was the most junior person presenting, but Joe really wanted to give me that opportunity and I...you know, ready to do it.

So Joe called shortly before Francis was born to check to see if I was going to be there the next day and, you know, tell me how important it is. Then he called again to say I shouldn't have pushed you. If you want to stay, it's totally fine. And then I quit answering the phone at that point, and then Francis was born, and everything was going really well, and I was working on my talk in the room, and she was sleeping on my chest. And then the next morning we were scheduled to be released,

you know, and go home with Francis, and I had to go give this talk.

And so, we conspired to try to stay a little longer so that I could run from Cary, North Carolina to Chapel Hill, North Carolina, which is about 25 miles, and give my talk. And so, my colleagues being much more senior than I all ran over, you know, ridiculously so. One senior person who is now a chair of a very prestigious psychiatry department, instead of three minutes, it was 25. And so, I'm like, wow, you know, I really blew this because I'm going to miss seeing my daughter go home.

But Tom actually said, well, you know, I want to see this because the title was on the social brain, and so they bumped me up, and I gave my talk, and then I promptly left and went back. And Tom emailed me the next day and asked me for my slides, and apparently said something nice about the talk I gave to the chair of the psychiatry department because the next day they offered me an actual faculty position as opposed to -- and he cited, you know, that he had talked with Tom Insel.

And so, thank you very much. You actually got me my first job.

Now, when we got back to the hospital, the social worker was very concerned that I wasn't there when it was time for checkout, and I got quite the lecture from the social worker. But we got Francis home, and, you know, it was really a very, very, very exciting time. Francis had, you know, a number of strange things happen during the pregnancy with Francis, some infections. She was turned upside down. They did everything they could to move her so she was in the correct position to be born. She was born by C-section. But for, you know, all the world a very healthy, happy little girl, just absolutely delightful. And I realized what it felt like when she was born to be willing to take a bullet for somebody, and before then I, you know, just didn't really see the world that way. I don't think anyone who's not the parent, especially, I think, the parent of a little girl, can really -- and I apologize if that's sexist. But there are heartstrings that are pulled when you're the father of a little girl that I think are very,

very, very profound and important.

So at the time, I was having -- you know, doing my career and excited, and I saw the career as something very meaningful to me. And I had the opportunity through Joe Piven, who's really responsible for getting me into autism research. I had been a basic developmental psychologist, and so I was working on building little eye tracking hats that go on babies' heads so I could monitor their point of gaze, you know, on a television screen, for example, and was very excited about doing this basic developmental work. And then I met Joe, and he talked me into applying that to autism, so this was actually the first paper published using eye tracking to measure point of regard in autism.

And it's kind of a funny story because one of the reviewers on this was Ami Klin, and I had just absolutely adored Ami Klin. And he was working on the same type of study, and so he actually rapidly sent his in for publication. I reviewed his and he reviewed mine. I won't say who finished their review first. I was a grad student, so I had more time. But we then simultaneously published in

different journals of course, you know, without the other one knowing. It will become apparent as to why he and I both know about each other's review later.

So, and we showed frankly what any good clinician could tell you about autism, which is that part of it is not making eye contact. These little red dots here are where an adult -- where several adults with autism actually view the face, preponderance on the mouth or other kind of incidental features, versus typically developing adults, which -- and this is a pattern that emerges in very, very young infants. They look at mostly the eyes and look down at the mouth every so often. And actually as an aside, totally doesn't apply to Francis. She's always made great eye contact, but we'll return to that.

Now, the other thing that I had been working on was studying what's come to be called the social brain, and I'm biased, but I would argue that this is one of the most important neuroscience discoveries in the past 20 years, kind of fleshing out what is the social brain. This started long

before me that I was able to ride this tide working with Greg McCarthy, who's one of the earliest investigators to use fMRI to study different aspects of cognitive function. And I came in with an interest in social cognition, and so he and I began to do a lot of work.

For example, trying to figure out what parts of the brain process the movements of other people versus the movements of other common objects. And so, I really didn't think of this work as being applicable to autism at all, and, you know, certainly at this point while we were concerned about different aspects of my daughter's development, I really wasn't thinking of putting the two together. And so, I was very fortunate to publish an early imaging paper showing that this little portion of the temporal lobe was quite specific to processing human actions, and later we discovered human intentions. So it's a wonderful building block for understanding other people, and it turns out that it has quite a story in autism, and I'll show you part of that story.

So this is simply showing you the double

association between processing the posterior/superior temporal sulcus to the biological stimuli versus botanical, and then a nearby area. One of the amazing things about the brain is these nearby areas that do incredibly different things. And this is Area NT, which is sensitive to all types of motion.

So my point in showing you this is this is where my research was going. And in a parallel universe I'm dad, and we're worried about daughter, but autism never entered my mind. And we were worried because she wasn't responding to her name very well, you know, as a couple of years went by. She seemed not as interested as she should be in people around her, having a hard time learning to crawl and walk, a lot of developmental delay, a lot of hypotonia, some aspects with the way her eyes were developing, so all subtle features. But even though we were in North Carolina, which has fantastic autism services, no doctor was saying this might be autism, right? And I'm working with one of the best doctors in the world, Joe Piven. But in my head, you know, keep business and family

separate, and, you know, so I actually never asked Joe, you know, what he thought or to look at Francis. Sometimes when your mentor, you know, you just don't feel comfortable doing that. I've gotten over that, but we didn't. And time went on. Time went on.

So I had great opportunities as a result of having the opportunities with Joe Piven and Greg McCarthy, and thanks to Tom for suggesting somebody should hire me. And so, I had the opportunity to move to Duke. I had done my post-doc between Duke and Carolina, so I had lots of strong opinions about basketball. And by the way, my cousin played for Kentucky the year that Duke and Kentucky played. Most of you in the room have probably seen the tape over and over again on ESPN Classics of my cousin standing flat-footed while Christian Laettner shoots it over his head. So I felt the need to go to Duke and save my family's name.

[Laughter.]

Dr. Pelphrey: And so, I went to Duke as an assistant professor and started doing this work, and that's when the kind of family, Francis, the

saga with Francis really came into being. At one point in the school systems in North Carolina, even though they have access to teach some really state-of-the-art science, they weren't up to par for my daughter. And it ended for me in them suggesting she go into kind of a behaviorally handicapped isolation -- isolated room separate from the regular classroom. And me arguing, well, you know, I don't really see this, and we didn't have an autism diagnosis, and so it was really just developmental delay, and she wasn't going to get any of the types of services that she needed.

And I knew from my developmental psychology training and my clinical friends that she needed things that were like what a child with autism needs, and she certainly wasn't going to get that with what they were proposing to us. And so, at about that time and these are pictures of Francis. It isn't often that you get to show pictures of, you know, like the love of your life, and so here she is. That's me when I had more hair.

And I should say one of the things that was going on with Francis is a lot of collecting

behavior, so a couple of funny anecdotes about that. One is that she became -- she loved the Teletubbies for a while, and that was kind of a miserable period.

[Laughter.]

Dr. Pelphrey: But she was -- I said in passing that there was a brown Teletubby. She asked me about the different colors of Teletubbies, and I just read them off, and there isn't a brown Teletubby. But she heard Dad say there was a brown Teletubby, and so there is a brown Teletubby. And I drove around to every place on the planet looking for something that kind of resembled a brown Teletubby, and then I got a yellow one, and I dyed it brown with the fabric dye that you can get in a washer, and subsequently dyed every other piece of clothing in the house brown because I didn't know how to get it -- my wife is shaking her head because she knows I can't do laundry.

[Laughter.]

Dr. Pelphrey: So she had a brown Teletubby, and her dad had brown hands all the way up to here. And she walked around -- at that point she was talking

a little bit, and she would say "Cocoa, Cocoa," and show it to everybody because she asked me what the Teletubby's name was, and I said, "Cocoa." So that a lot of hoarding behavior, and you can kind of see this here.

The social aspect of Francis, that's not where you think autism. It's really the insistence on sameness, the emotional regulation difficulties, the collecting. And her first word actually was a result of -- she and I would sit together and watch "Wiggles," and Henry was her favorite character. That's Henry. And she kind of pointed that she wanted Henry and said -- you know, in my head said "I want Henry," so I ordered Henry and Henry arrived. And she opened the box, and she grabbed Henry out, and she started running as fast as she could. She's always been very, very awkward and hypotonia and screaming, "Henry, Henry, Henry." And then that was very exciting. And then her mom said, I'm going to take Henry, teasing with her, and she screamed, "No, no, no, don't take Henry. Bad mom." And it was just like, whoa, you can talk. All right, great. This is fun. And so, from that point

our house started being filled with different toys.

I am not clinically trained. I don't really know the concept of putting a child on an extinction plan, but I'm learning. My instinct was, well, if she wants to talk about and categorize the toys, we'll get them, and we'll talk about them, and categorize them. And she's always used these different characters, these different shows, in an interesting way to kind of navigate her world, and I'll show an example of that in a little while. So that's Francis, and I lost my train of thought because I'm talking about my daughter.

So schools. She was about four here, and this was still just a little bit before anybody was giving us the word "autism," right? And I know it seems inane that I wouldn't think of autism, but sometimes you just don't see it even if you're studying it. And at that point it had been made loud and clear to me by my department that I wasn't going to be promoted by studying autism, that they really wanted me to study basic social cognition. And when you're an assistant professor and brand new in a department, I was terrified. And so, I was

taking myself out of the autism equation, mostly for fear of not being promoted, I hate to admit it, but also because it was such a complex problem, and people were already working on it and doing a lot better job than I was. So why would I try to compete there when I could write all kinds of imaging papers about the development of social cognition in typically developing kids?

So I was out of the autism equation, and I went and gave a talk at Carnegie Mellon, and met Marcel Just. Most of my life -- I would argue, most of my successes in life have been because I met the right person at the right time. Extremely fortunate. I think I have like "help me" written on my face somewhere --

[Laughter.]

Dr. Pelphrey: And so, people tend to help me at really critical -- Annie is shaking her head like, yeah, definitely. But, you know, or said positively, I think I can be mentored pretty well to a point, and then I get very bullheaded.

So I saw Carnegie Mellon, and in Carnegie Mellon right about here on the back side is this

amazing school called the Carnegie Mellon School. And while I was there giving a talk, the department head said something about, you know, we have a job opening, maybe you'd be interested in it. And in the abstract I'm perfectly happy at Duke, you know, but my daughter. And so, he had me meet up with the -- with Sharon Carver, who runs the Children's School at Carnegie Mellon. This is the best school for the four- to seven-year age range that you could possibly find on the planet I submit. I mean, it's run by somebody who worked with Donald Hebb and studied cognitive psychology, and is fantastic with children. So she was given the opportunity to set up a school for kids that's really perfect, and I was sitting in it and realized it was perfect for Francis.

And so, when I had the kind of debrief at the end of the day with the chair, I said, if you would -- I know that spots are limited, but if you would give me a job and a spot for Francis in your school, I would move here, and I had some grants at that time, and so it was an easy sell. And so we moved. We packed up and moved to Pittsburgh.

I think people on the outside that don't really know me very well, I've moved three times in my career, which is probably a little more than average for somebody my age. In each case I was able to secure something I wanted for my family. I think it's oftentimes seen as sort politically moving so that she can get more and more and more. Sure, I understand how that system works in academia, and I've tried to use it in order to help Francis and help my sons, and so I say that shamelessly. I think anyone in my position would. There are very few things that I'm particularly good at, but I've been blessed with being good at science, and so I've used that to get these opportunities for Francis.

Francis excelled at that school. I mean, it was amazing. And finally we got to see someone who started to use the word "autism." I teamed up with Nancy Minshew, another mentor, another person that I met at the right time, and she sent me to see -- after meeting with Francis for a few minutes, you know, on a Sunday afternoon, suggested I go see people at the Children's Hospital there in

Pittsburg, and we got a diagnosis of autism, and I was floored. I can't tell you how stupid I felt that I didn't see autism. You know, girls don't get autism. It's a male to female ratio, and I could quote all the statistics. She makes eye contact, and it's this, and it's that. No, we're pretty sure she has autism.

And you realize at that moment in your gut, yeah, that's absolutely it, and I still don't know how I feel about the diagnosis. Scientifically, what does that give us? Well, from a parents' point of view, it gets you a starting point, a name. It quickly becomes a curse and a positive, but it sort of gives you a place to start. So Francis has autism.

Okay, next person in my life that I'm meeting. First off, Bob Schultz had decided to move to the University of Pennsylvania, and Ami Klin had to remember that he reviewed that paper and had been following some imaging work. And so, I got a call from Ami Klin. Probably everybody in this room knows who Ami Klin is. Fantastic clinician, fantastic scientist, and a great person, and he

said, we have an opening at Yale. And I recognized Yale as -- a funny story. When the Start Centers were funded, Carolina got one. Joe Piven and I were involved in writing that along with another group. It was my first grant writing experience, and I wrote the imaging project for it. And then Yale also got one.

Yale put a release in the *New York Times* that they got the best score of all the Start Centers, and that's kind of a Yale thing to do. And, you know, I was so mad because we had heard each other's scores, and Carolina's was a little higher. I don't think Carolina got the best score either. And, you know, Joe assured me it doesn't matter. You know, Yale is prominent for autism. They need that. And so, I was mad, and so I had been following Yale and autism hoping we would just match them in every area.

And science is about competition as much as it is collaboration, and I wanted to win. And so, when my former nemesis called and said would you like to come to Yale, you know, we have an endowed chair, it has job security, and we'll give you tenure. And

so, I thought for about five minutes, and then I knew I was moving to Yale. I loved Pittsburgh. I loved Carnegie Mellon. But this was a great opportunity. Well, you know, I went home and talked it over with the family. Well, let's proceed with caution.

And so, Ami, being a brilliant clinician, knew that if he could just get Francis in the clinic, the deal would be made. And so, I knew Yale had like a two-year waiting list and said, well, I'd love a second opinion on Francis. So Ami Klin and Fred Volkmar became Francis' physicians, and that's like somebody -- I don't know anything about baseball. I played soccer. So that's like Pele coming in and helping out your kid with his left foot, okay? Yeah, this would be great. So I go in, and they were amazing. It was just fantastic. And I knew at that point, well, this is a place that I can really build a program. This is home.

So we packed up. We moved and settled in. And I show this just because for the first time since Francis really started having troubles as an infant, it was happiness. We're really seeing her

improve. We had the right resources. I am extremely blessed, and I realize for other parents listening to this and in the room, the rest of you don't have Ami Klin to show up at your kids' IEP meeting. When Ami Klin and Fred Volkmar show up anywhere in Connecticut to an IEP meeting, the school does whatever they tell them to do if they have to move mountains.

And one of the real challenges and frustrations with the school systems, and I believe they mean well, but, for example, in Connecticut from town to town, totally different philosophies. It is the truth that some towns, Guilford, Connecticut, and their system are fantastic for kids with autism. They put a lot of resources into it, and that's where we chose to live for Francis. Other towns put the money into a legal defense fund so that when parents ask for things, they say, you'll sue us, and most of the time the parents, while they're paying their property taxes, don't have enough money to sue the school which has access to said property taxes and is suing them for services. This is a major problem. I won't say a lot of political

things today, but that's a major -- it's disgusting.

And so, you know, when -- fairly simple. Nothing that Ami and Fred were suggesting was really outrageous at all. You know, make sure Francis has some one-on-one help. If a fire drill happens, make sure somebody walks out with her so she won't bolt. All of those little things. But I realize how lucky I am because of the science I do and the reputation of being invested in autism, and I wish every parent could have that. And so, that would be a major outcome.

Okay. At Yale we started -- what I didn't like about Yale's program and what I've had license to really do, Yale was renowned for diagnosis, earlier and early diagnosis, better and better diagnosis, taxonomy, figuring out how to cut up the meatloaf, you know, what are different types of autism, all of that. Very important stuff, but what we weren't doing was treatment in any real way. So if you have early diagnosis, why not early treatment? If you have strong genetics resources from that state, why not genetics on everyone? If you have imaging, why

not image every child that walks through the door, electrophysiology? Why not do it all, but use treatment as a natural experiment because we know enough about treatments at this point that we're not going to hurt any kids with autism with any of the empirically tested behavioral treatments that have shown some promise. But what we don't know enough about is how those treatments work. We don't know how any psychiatric treatments work really, but particularly behavioral treatments in autism.

So what we set up was a system, different components, where we could keep doing the basic work of looking at social and cognitive functions and looking at the neural genetic sub-traits, so mapping out what the brain does in typical development, looking at large-scale individual differences. And here we're talking about trying to look at populations of individuals, so, for example, if we want to make early diagnostic procedures, looking at those people with increased genetic risk, for example infant siblings, is the first step. If you want to make a real diagnosis test, it has to work no matter what your base

strait is, so it can't just work on people for whom you already know they're at high risk. It's got to work on the low risk kids, too.

So we take a developmental epidemiological approach to much of what we're doing, which is consistent with where NIMH is headed in terms of an RDoC approach. You can do it all in one fell swoop if you throw out the notion that you should only focus on those with the particular disorder.

So bringing in that aspect, taking our basic science and trying to develop treatment protocols for specific targets. And this is borrowing from Dr. Insel's championing of this, this idea that you can use neural systems level measures, like the readout of an fMRI scan, as your target -- and I'll show you a couple of examples of that -- and then use these test efficacy test target engagement. And if this works really well, you can roll out evidence-based treatment back at the population level.

So this is the model of the work that we do, and this work is really based on the notion of I'm not being happy with the services available to

Francis. You know, Yale had a great reputation for diagnosis. I want it to have a great reputation for treatment development, and a unique kind of treatment development. Not any one brand of treatment. I don't want it to be associated with a particular form of ABA. I want it to be associated as the place that all treatments come, some survive, others ring the bell and go home. And we'll use cognitive neuroscience methods to really test, and then even those that fail will know why they fail. And I think where this is going is most will fail for some kids, some will fail for many kids. We can tell you why they fail. Failure is a great way to learn.

Now, talking about individual differences. So I'm actually the father to two children who have an autism diagnosis, and autism runs strongly in my family. I have numerous nieces and nephews, so it's a family affair. But what fascinates me is the difference between -- so here's Francis. This is Lowell. And he was diagnosed very early on as a result of being, what I assumed, was a typical kid in an infant high risk study, as being somebody to

really watch, a great deal of concern. And that emerged into a PDD-NOS diagnosis, which we now talk about autism spectrum disorder. Not as severe as Francis and very intellectually gifted, a little shy, a little nervous, a little awkward socially, and has lots of intense interests. One of his intense interest is building things. And he has developed language quite nicely and has had massive, massive early intervention. I don't know if that took him on a different course, but he's definitely what people talk about as an optimal outcome child. So that fascinates me.

And then this little guy, the ham of the family, this is Kenneth. If there's like the opposite of autism in some three-dimensional space, that's him. Most socially outgoing, gifted. He's going to be president. Watch this kid. You should start asking him for things now because he's going to be in charge. Not at all shy. Fearless. Absolutely fearless. So very, very, very different siblings of Francis.

So we are very interested in studying siblings. So, for example, one of the earliest studies we did

with imaging was to look at children with autism and their unaffected siblings, and the Simon Simplex Collection made this possible. So we used fMRI to look for state markers. So this is brain regions that show dysfunction in autism relative to unaffected siblings in typically developing kids. Trait markers, which I think are probably one of the most interesting aspects of this work, regions where unaffected siblings and their affected child with autism sibling where they share a dysfunction. And then finally what I think is really cool, what brain regions help you avoid the genetic risk for developing autism? How do you compensate for that genetic risk?

And so, we showed these simple biological motion figures. We're seeing a person moving about playing patty-cake and then the scrambled version of that. And this is a beautiful probe for getting the brain to start doing everything it does when it process social information. And we were able to find these regions, and I'm going to give the more layperson's summary.

This, the state regions. These are all the

usual suspects of autism -- the STS, the ventral temporal lobe, ventral lateral prefrontal cortex, the amygdala. These are formed gyri bilaterally. No surprise here. These surprised us where they were located. When you start looking at the literature and you do formal meta-analysis, it's really all the regions that come up across neurodevelopmental disorders. So pick your favorite neurodevelopmental disorder. One of these yellow trait regions is in there. These are regions that are in the phenotype by definition for autism, but they're in the phenotype for other neurodevelopmental disorders as well.

At first this depressed me because I would hope that, you know, a genetic -- a neural signature for the genetic risk of autism would be specific. And then it occurred to me, well, why would it? No gene has ever been shown to be specific to autism. We inherit a risk for neurodevelopmental disorders, and this hearkens back to cocktail parties some friends threw for me. "Cocktail party" is too highfaluting of a word. A keg party that my friends threw for me after I got my Ph.D., and one of them

was like, well, development psychology, why did you do that. They just published the human genome. You're totally out of a job. Yikes, yeah, probably. My backup plan is to open a coffee shop. It's still on the table. I might do that.

But really we're not out of a job as developmentalists. That developmental perspective can answer the question of how do you come into the world with a set of genes that affects particular pathways, okay, so we can nail it down to particular pathways. But even then we look across disorders and see that different disorders share risk and differences in those pathways, so it becomes a when and where question. And "when" and "where" questions are great in neuroscience and development neuroscience. So I think that's the answer to the friend who was concerned about my employability.

Now, compensatory. This blew me away. If ever a development neuroscientist wanted to see two brain regions that show up in people who have the genetic risk for autism, but don't express it, ventromedial pre-frontal cortex and the temporal parietal

junction, two regions that have been nailed down as being involved in high level theory of mind reasoning about other people. It's tantalizing to interpret this as the siblings are accomplishing typical behavior, but they're using a different set of brain regions that allow them to do it that are brain regions that we normally use for more high level things than just processing whether people are moving in the environment and what they intend to do. So it gives you an insight into the life of a typically developing sibling of a child with autism. We might be doing a lot of work underlying that typical development that we're just completely unaware of, and imaging allows you to see that, especially developmental imaging.

Now, everything I've said so far is totally not true for girls with autism. Most of the brain imaging studies that have ever been done, mostly boys with autism. It's not because we don't like girls. It's because they're hard to find, poor imaging studies. And they're also messy in terms of the diagnostic categorization. Very few people are great at the diagnostic care that has to go into

kind of figuring out girls.

So, for example, when a boy presents and they're lining up trains, it's like, oh, yeah, you know, excessive interest. When a girl presents and she has 10 different dolls from the American Girl Doll Store -- it's a true story for Francis -- she can tell you a lot about each one, and they socially interact, and she seems to be doing pretend play, like sitting them down in a row and teaching them as a teacher. Well, that's not going to get her qualified on the ADOS, you know, or an ADI. But that's her version and many girls' versions of restrictive repetitive behavior. They're fixated social cognition, they might talk about their friends, their place in social hierarchies. They're fixated on it. They have social motivation, but they're talking about it in a way that on the surface of it is like a little boy with autism talking about strengths, which is very easy to pick up, so that sort of repetitive behavior.

So this is just a slide showing you that as we probe the genetics of autism in girls, we've seen

that there's a difference in the underlying genetics, especially in the type of hit that you have to have. It seems that one of the best ways to avoid autism is to be a girl, and that plays out in the genetics, and that plays out in terms of the social phenotype in the brain. Here girls with autism show robust activations throughout the social brain relative to boys with autism, as well as to typically developing boys. Where they're different is in comparison to typically developing girls, and as a father, that terrifies me.

So we took this interest in girls, and I found likeminded people at different sites when the Autism Centers of Excellence were being solicited. And so, we have teams from San Francisco and UCLA, Matt State and Dan Geschwind; University of Washington with Sarah Webb; Harvard with Chuck Nelson, Nadine Gaab; at Yale Jamie McPartland and myself. We lost Matt State to San Francisco, so we added a site. I went and looked for what I thought was the very best team that I could possibly assemble to get one of these networks to focus on girls. And that was one of the most exciting grants

I've ever written. It was so much fun to learn from Dan Geschwind and Matt State. They're extraordinary.

And we're in the middle of it right now, and I can't wait to show what the integration of genetics, and imaging, and behavior. And we very quickly realized that we couldn't use the gold standard diagnostic techniques, and so we threw in in our sample populations of girls that might normally be missed and we're trying to understand where they fit in. So stay tuned for that. In another year those papers will be coming out describing what we're finding. It's very, very exciting. I think this is the largest collection of girls with ASD as well as their unaffected siblings, and it's also a huge collection of boys with ASD. So we'll be able to find out a lot about sex differences.

So I told you my dream really when interacting with Francis is what can I know from science that would allow us to develop better treatments? And so, we went a couple of different directions. One was to go after pharmacological manipulations, and

one of the ones, oxytocin, intranasal oxytocin, was something that was being talked about by a lot of people in the popular press. There had been some brilliant science done on this, Tom Insel doing most of that brilliant science. And it was very attractive to autism researchers to go after this.

I was actually very suspicious. My understanding was that oxytocin doesn't get into the brain if you spray it into the nose, but I had a couple of colleagues that I respected and a post-doc, Ilinik Gordon, who kept chasing me around, wanting to do an oxytocin study. And I finally gave in, and I gave in because I had been getting lots of emails from parents saying that they had bought intranasal oxytocin online, and they were giving it to their child, and they think they really see a difference.

I can assure you while I have a public platform, if you buy oxytocin on Amazon.com, by the time it arrives at your door, if it ever was oxytocin, it will no longer be oxytocin. And that simply spraying it into the child's nose is going to do nothing, and it may be harmful, depending on

what it used to be before it was an oxytocin. So please don't think I'm endorsing in any way intranasal oxytocin as a treatment for autism.

That being said, our data were interesting. So we gave oxytocin once to kids with autism or a placebo, a double blind placebo controlled study, prior to going into the scanner. So remember, we had a particular target, and our target was the social brain. We wanted to see if oxytocin would alter the social brain function, and in response to a simple stimuli like these, look at the eyes and tell me whether they're hateful, thinking about something disgusting, or worried. And then a non-social judgment, look at the headlights of the car, tell me if it's a sports car, SUV, truck, bus. The kids in the magnet, made sure they could do this task.

When we looked at oxytocin versus placebo, it's exciting from the point of view of relative to placebo, we had much more activation in these classic social brain regions, also in reward centers in the presence of oxytocin in response to the social stimuli relative to the non-social

judgment. In placebo, we saw what we would normally see with reference to typically developing individuals, so reduced activation in autism some, but reduced particularly when compared to on oxytocin.

Lots of interpretations for this. We're not going to get into that. But one of the sort of exciting findings was in particular there were regions, especially regions that are well known for processing reward value of stimuli and their connectivity to these temporal lobe regions involved in processing social meaning, were increased, but only for the social stimuli by the presence of oxytocin versus placebo.

So what do I make of this? It's interesting to me, you know, obviously the next step in oxytocin research would be to develop compounds that we can take, easier to deliver than intranasal oxytocin that alter oxytocin centrally. But even more so I think is the contextual nature of these effects. There was a paper in *Nature* about a week ago showing that you actually increase dislike for the out group in the presence of intranasal oxytocin.

Very subtle. From the beginning of this research, it's all about the context. So this should be very important for autism, not just studies of oxytocin, but drug studies in general.

There's a model where -- I think where experimental therapeutics is pushing us to control the context under which the drug is delivered. So instead of having a study where they come in, they get three doses about the same time of day for six weeks. There's a little bit of measurement of what treatment might be going on in the background, but it's an FDA drug trial focused on drug.

I think where we'll gain much more leverage is if we team up neuromodulators with specific empirically-based behavioral approaches so that we can control the social learning that happens, give whatever compound we think of as a neuromodulator, a cognitive enhancer, social cognitive enhancer, in the context of that training. And that's when I think that we'll actually see some really cool effects and some synergy between the neuromodulator and the behavioral treatment.

But I want to show you some work that we're

most excited about right now, simply looking at a behavioral intervention. So pivotal response training is one form of ABA that has been expanded to be much more general, much more targeted towards generalization and natural environments than what you typically think of as ABA.

So my colleague, Pam Ventola, has led this work. She's a new assistant professor at Yale, and one of the smartest hiring decisions I've ever made. This is Hannah, one of our research assistants. She's working with a child with autism.

[Video presentation.]

Dr. Pelphrey: So this is what pivotal response training looks like. She's really hoping to get some eye contact doing something that the child really likes to do. Clinicians in the room. You're seeing the parents that have worked in this type of treatment. It's very familiar. So doing something that's very, very engaging.

Here's another little girl with autism, a little girl.

[Video presentation.]

Dr. Pelphrey: Okay. It's always risky to do in

a talk. Anybody notice any differences between those two kids behaviorally? Shout out. Yes?

Speaker: [Off audio.] Bubble, babble.

Dr. Pelphrey: I was wrong, boy. But, yes. Yes. Okay. The second boy was more jumpy. That was one I was looking for. More jumpy. So we looked at and scanned pre- and post- about 24 kids, four to six years of age, moderate to high functioning autism, and very well matched for IQ and whatnot against a weightless controlled group and against a typically developing group.

Now, the results -- let me just show...you know with a kind of with a grain of salt another episode.

[Video presentation.]

Dr. Pelphrey: This is after six full weeks of treatment. Eye contact, that's what we were looking for, so exciting. It turns out on behavior, these kids do a lot better. This is nothing new. Actually it is a bit new in the sense of we're very rigorously testing a form of ABA. I hope I don't anger people, but I would argue that these forms of treatment, with some exceptions, like the Denver

model, have not had the type of scientific scrutiny that they deserve. So first thing we wanted to do was see if in our hands, you know, sort of calling our shots with an outcome measure like the Social Responsiveness Scale, could we see a difference, and the answer is yes. So they work. They work for some kids. They work a little bit for most kids. They work great for a few kids. So this is showing you that the total SRS score goes up, and every sub-domain of the SRS adds to this. It goes up very nicely, so behaviorally it works.

The brain findings blew us away. So the kids came in differently from the start, so about half the kids. It's nice when that works out that way. About half the kids totally defied everything I believe about social brain function. They were hyperactive in social brain function, so that was problem number one. Oh, boy, the results are not going to replicate. The other half of the kids, beautifully behaved. Their brains showed really nice hypoactive results.

This didn't vary by boys and girls. It was a mixture of boys and girls in here, so it wasn't

that. But when we started studying this, my post-doc, Daniel Yang, wouldn't accept my solution, which is let's just reanalyze the data, make sure we're not making a mistake because we can't be wrong. He kept saying I already analyzed it, you know, it's not wrong. But I've noticed having seen a few of these kids walking down the hall, that those are the hyperactive kids. Whoa, whoa, wait a minute, don't say another word.

So we got the clinicians to code blindly which kids were exhibiting different behaviors and giving us their input, and then we looked in that for verbiage like "hyperactive," "hypersensitive" all over the place, things like that. Well, it turns out that our brain imaging data lined up beautifully with the behavioral impression. Very difficult to manage clinically, kind of very all over the place. So we think we found two biotypes, one a very classic picture of autism, not interested in the social world, social brain hypoactive; the other strongly responsive to all stimuli, social and non-social, all over the place. There was this whole -- I believe it's been

popularized too much, but there's an intense world.

These are certainly kids that are like Francis, as I mentioned earlier. Social hasn't been her problem. The intensity of the world seems to be her problem. So, for example, her biggest fear in life is the birthday song, which has an element of social, but also attention placed on her. And she will run across a crowded street very rapidly if she hears the birthday song. So I think she's one of those hyperactive kids.

I forgot the punchline. Their brains all ended up in the same place, okay? They all ended up more like typically developing kids. I was disappointed in that because I wanted to see some compensatory activity. That would've been scientifically very exciting, but the way they ended up in that same place differed over time. So if there were repeated scans, what we're able to see is when the hypoactive group normalized, it was the result of an increase in activity in the ventral striatum and the amygdala, and nucleus accumbens.

Classic regions involved in reward and motivation and their functional connectivity to the

rest of the social brain, but only in that subgroup. In the other subgroup, reduced activity in the thalamus and its relays to primary sensory areas as a result of the treatment. Leading to in the end, brain differences that were basically indistinguishable, and indistinguishable from typically developing. And these kids were doing quite well. We didn't cure autism. That's not something we talk about, but we alleviated a great deal of symptomology, and the brain followed suit.

This shouldn't be surprising. All behavior comes from the brain, but what's important about it is that we can say, well, these kids are different at the beginning. Now, in our next study, what if we modify the treatment for the kid on entry into the scan because you can see these things in the level of individuals. Because we've scanned so many kids, we know what kids should look like almost in a growth chart kind of way. And so, we're hoping to test that next, and actually alter the treatment, have different arms, depending on who comes into the door.

And what we're finding is that the therapist

did that anyway. Even though there were strong guidelines, we don't mandate every word that's being said, so for the hyperactive kids, and they're very difficult to manage clinically, the therapists were working quite a bit on emotional regulation and aspects of that, whereas for the less socially motivated kids, who were very easy to interact with, very calm and subdued, they were working more on eye contact and then improving social motivation. So, okay.

Now, I've been spending too long on science. Let's get back to Francis. So Francis now has been doing great until fairly recently she had her first seizure, and only a scientist dad would take a picture of his daughter the night after the seizure. But it's a scientist dad who has access to Laura Mint, who's a fantastic child neurologist and took care of Francis. This was me. This was the longest night I've ever spent because I'm not an M.D., and I assumed the seizure could be life-threatening because of what you can read on Wikipedia. And so, I stayed up all night watching Francis, and I took pictures of her every time I

thought her skin looked a little blue and sent them to Laura Mint, who undoubtedly woke up every time, looked at the picture and said, you don't have anything to worry about, Kevin. She was very nice about it.

But Francis had a seizure while she at school in math class. Math is a very stressful class for her. One of her crushes is in there, and she had a seizure, and it was her first. And this is her getting tested the next day after a sleep deprivation period, and you can just see the fear. Francis lost a lot of gains after that happened, and that's common as I understand it now. Francis was going through puberty, which is, I understand now, common for a first seizure to happen. And the statistics are very comforting, but it was a very, very, very scary period.

And, again, I felt like a heel because I had excluded systematically all kids who had had seizures from my imaging studies for the past 10 years because that would make the data too messy, but I apologize for that because I really learned a lot. So we study seizures now.

In particular, this sets up for me talking to you about a very particular form of autism, severe late regressive autism. This used to be called childhood disintegrative disorder. It's very, very rare. Now, we talk about it in more dimensional terms as kids who are typically developing for a long period of time, develop language or doing really well, and then regress. And so, I want to talk about those kids and tell you about our efforts to scan these kids, who almost always have very, very, very low IQs after the events, after the regression.

And, you know, it's interesting from a geopolitical point of view. These are the kids that most make you concerned about environmental influences, you know, vaccines causing autism, these types of things because they were typically developing, and something catastrophic happened, and now they have autism. So we looked at these kids through imaging and through genetics, and I think you'll be interested in what we found.

So this is a great finding from a Wellesley paper in 2013 showing that when you look at gene

expression and you do co-expression network analysis, in autism you find pre-frontal and primary motor cortex, layer five and six, early- to mid-fetal development. So what was brilliant about this paper was it nailed down in kind of the average cases of autism when and where in terms of brain development, right?

And it actually puts to rest a lot of questions that are tricky questions and says, you know, genetics, early in development -- early in fetal development. Relieves parents of a lot of pain of did I cause this, you know. Still aspects of any time I go to the grocery store, well, if you were only more this, your daughter would be less out of control, and it's like no. So great, great paper.

We did the same thing in our cohort, CDD families, and so we had 32 CDD families. This is a disorder that appears at a base rate of about one in 100,000, so extremely rare. The gentleman who ran the Child Study Center long before I arrived, Donald Cohen, had a strong interest in this and started cultivating these families. So we were able to go back and we were able to look at their brain,

wide age ranges in that data, and look at their genes, and try to find genes for severe late regression.

And we found a collection, and when it seeded it with high confidence autism genes, we found that they tended to be expressed in different places than other high confidence autism genes. So CDD genes are being expressed in the thalamus, amygdala, hippocampus, and cerebellum as opposed to pre-frontal cortex, and later mid to late fetal development. About the time we started doing this study, we had some other data available from the Non-Substance Lab so we could look more carefully at a wider set of brain regions and look where these CDD genes are expressed. And one of the interesting things that we found was, again, confirming the cerebellum/thalamus connection, the hippocampus, striatum amygdala. But seeing an over expression of the CDD genes earlier, later than typical autism, normal autism, and then another over expression in the amygdala and hippocampus fairly late in develop. So this is well past birth in age ranges of where you tend to see the common -

- where you most commonly see the severe catastrophic regressions, so ages four, five, six, seven, okay?

Now, so that was exciting, but does it map on in any way to the brain? So to do that, we needed to scan these kids, some kids, some adolescents, some adults all with intellectual functioning in the severely intellectually disabled range, non-verbal kids. And so, we went through all kinds of procedures to get these kids scanned, including a lot of mock training, putting them through what we were going to do and practicing. And we were able to scan most of those kids. When we did, we did a very classic face versus place comparison, which gives you a beautiful signal in the social brain. I was particularly interested in hitting the amygdala, and this is a great way to hit the amygdala.

Now, what we found is that in hippocampus, cerebellum, thalamus, we were seeing the same regions that were implicated by the genetic analysis, completely separate data playing out in terms of where in brain function these CDD kids,

these severe late regression kids, are showing brain dysfunction, in this case too much activity in response to a face versus a house. We also eye tracked them, and their eye tracking patterns are different than, you know, if I may, run of the mill autism. So this is a very classic finding, high functioning autism, looking pretty equivalently at eyes and mouth, less at the eyes in typically developing people. Typically developing people, high functioning autism.

Low functioning autism actually doesn't really follow that classic eyes, mouth distinction probably because of not using the mouth to facilitate social communication. CDD kids make great eye contact, if anything a little more so than typically developing kids. So we're putting them together in a spectrum, but these kids are actually showing some really interesting properties, different brain areas that are affected, different genetics, different eye tracking patterns in terms of quantifying the social phenotype.

So that's become a major aspect of our work.

Stay tuned. I'm really excited about those particular findings, particularly given I think it's one of the first times we've seen convergence between the genetic prediction and where you should see a difference in a sub-population of people with autism, and then seeing that on functional imaging, that predicted difference. That convergence is unique in a sub-type because we have to deal with the heterogeneity of autism in order to begin to make progress in terms of treatment.

So the last thing that I want to tell you about -- this is Francis as a very, very little baby, just playing with her. Trying to help her learn how to rollover. So, you know, one of the things that most haunts me is why didn't I know early on. I had worked with Grace Baranek when I was a graduate student coding videotapes of early interactions. Why didn't I know?

So we developed the methods to scan babies both with optical imaging -- you see here a little hat they can wear and actually interact with people -- and with fMRI. That's Lowell getting his first fMRI scan. And we've developed a marker using this

biological versus scrambled where we can tell the difference between high and low risk kids based on whether or not their sibling is a child with autism, high risk their sibling if they have an older sibling, low risk they don't. And we're able to see that simply by measuring the blood oxygenation level response over this STS region that's become so important to us even at three months of age.

So very exciting work. We have to point out, though, that this is just measuring risk. Most of the kids in this sample won't develop autism. I want to know why. Why if you're coming into the world early on according to every developmental theory we have, your behavior should be canalized, and you should become more likely to develop autism, but there are some kids that jump that trajectory. Love to know why. It's such an obvious science question, but we tend to focus on other aspects.

And I want to show you one other thing. So Francis now is very much a young woman. She has always -- so she's 11. She's become interested in

boys, which I'm dealing with. One of the things with Francis, we talk about everything, and so now we talk about her crushes. And don't get me wrong, Francis doesn't really have or Dad doesn't think she has the concept of exactly what a "crush" means other than for whatever reason she's interested in that boy.

So whereas she used to collect toys and different stuffed animals, American Girl dolls, now she collects crushes. So she downloads pictures of, you know, all the guys from *Grease*. She has a crush on most of the guys from *Grease*, except for John Travolta because she thinks he's too goofy looking.

[Laughter.]

Dr. Pelphrey: And she puts them on her walls, and she lines them up. And this is quite the experience, you know. I could deal with Lowell lining up dominos, and knocking them over, and kind of thinking that's really cool. I could deal with having to buy all the Teletubbies, the collection, and then finding a place to put all of them. It's different to kind of worry about how is she going to navigate this because the boys haven't gotten

interested back yet. I've got a couple more years.
So short of buying guns --

[Laughter.]

Dr. Pelphrey: -- you know, there is like, well, how do we kind of navigate this. And these are pictures of Francis with some of her friends. This was her first day of middle school. This is as close as I could get. She wanted to ride the bus, and so she's been doing really well at these things.

So Francis loves now *Grease*, and I'm like why does she love *Grease*? She watches it over and over and over again. And, you know, what else would you watch to kind of figure out the world of boys and girls, and cliques in school, and how you fit in, and how do you become a Pink Lady. And, you know, fashion is a big thing for her, and so I love taking her shopping for cool sets of clothes. Everything seems to turn out pink. But, you know, so that's what she's doing these days.

And you look at this and you kind of think about the brain. One of the things I worry about and one of the things that's come up since middle

school is social exclusion, you know, and it hurts for me to watch her get socially excluded. She's a little strange. She's very lovable and very friendly, but she can quote *Grease* all day, and if you ask her a question, she'll answer it by quoting *Grease*. That's going to get her into trouble with other girls who are much sophisticated. And she tends to have imaginary friends that she talks to. And so, you know, we've been doing studies where we look at social exclusion, and brain science can tell you a lot about what happens and specific to autism why kids with autism might be upset when they're socially excluded.

So cyber ball is this game that cognitive neuroscientists have come up with to study this. And you have somebody play with two other players, and you just throw them the ball, and every so often they exclude you. And what's brilliant about this is that it actually leads to brain changes in regions that process pain. And so, the argument has been that they're feeling the pain of social exclusion. We thought an important game for autism would be cyber shape where there's a rule if, you

know, your ball is a green diamond you throw it to the guy with the green diamond. If it's a blue circle, you throw it to the blue circle. And now if someone is excluding you, it's nothing personal. They're breaking the rule, right? It's another layer of it.

And you might guess that in the case of typical development it's the social slight that really gets these pain centers activated. In the case of autism it's actually they broke the rule. And so, again, same result, same behavior -- you know, I felt bad -- but different brain, okay? Sort of challenge you to think about that in terms of trying to understand people with autism and where they're coming from.

And the very last thing I want to say is a shout out to Kenneth here who really has to deal with having a dad that studies autism, a sister with autism who embarrasses him at times frankly, and he wrestles with feeling embarrassed because, you know, his dad is not embarrassed, and he's trying. And he's a very sensitive young guy, and he actually has a theory of autism that is all about

anger issues. The most important aspect to him is when his sister loses her temper, and this is a pitch for more studies of emotional regulation in autism frankly, and I think Kenneth is onto a very good idea.

And this is just to tell you that there's a lot of hope here for people with autism who have some fairly strong verbal abilities. Cognitive behavioral therapy, this is my colleague, Dennis Godosky's, work. We're doing this in the context of an RDoC study that we have individuals with autism coming in as well because we don't exclude anybody. We want all of the different diagnoses involved.

And when we give cognitive behavioral therapy to work on anxiety and emotional regulation, we see in these individuals these beautiful increases in pre-frontal cortex activity and regulation of these lower limbic areas, and these are in older adolescents. The same is true of adults with autism.

So I want to leave you with this. So Francis is now part of a huge blended family of five kids and two adults, and she's doing great. I want to leave

or start the scientific argument that we actually know a lot about cognitive neuroscience now. If we keep going in the direction that we're going in, cognitive neuroscience of autism, we can use it to more effectively develop therapies that will help children across the spectrum and across the age range. And probably the most fertile ground will be adults with autism, and we can do a lot in adolescents and adults, especially young adults, where we still connect with them by virtue of leaving school and possibly going into college and their first jobs, and facilitating that.

So very, very exciting times. I'm very hopeful. I feel like I'm getting old because I guess I've been in this business now for 11 years, so every time I see Francis, I'm reminded of how long I've been doing this. But, yes, I really appreciate you letting me talk about my family. And there's Francis, and, you know, she never saves anything for the swim back, so I'll leave you with that thought.

[Applause.]

Dr. Insel: If we could take a couple of minutes

for questions.

Speaker: I'm interested especially in the population of autistic children that actually make contact with eyes and mouth. Do they seem to be more sociable, getting the sociable cues? I'm suggesting they do because isn't that what they're trying to get to?

Speaker: Can you repeat the question?

Dr. Pelphrey: Yes. So the question was the population of kids, not everyone with autism makes very poor eye contact. Are they showing higher levels of social functioning, and there are sort of two answers to the question. One is let's pretend no major interventions. When you look at very young infants and follow their eye gaze over time, it is the case that the amount of appropriate eye contact measured with eye tracking predicts later social function. And so, that's the purist answer to your question.

The other answer to it is there's so much intervention going on that sometimes eye contact will be made, but it will have a different character to it. So even though the eye tracker

scores it as they hit the eyes, in actual interaction, it's behind. It seems like a stare-through as opposed to true because it's not accompanied by changes in facial expression, and that type of eye contact doesn't a good job of predicting. So that the study that you need to do to understand the role of eye contact in the development of social function is the prospective study.

Speaker: Thank you so much. I wanted to ask -- I wanted to make a comment and ask several questions, but I'll do as much as you let me. First of all, I'll take a bullet from my nine-year-old with autism, a boy, for sure, so I think it's not just a dad/daughter. It's my son, Benzi, I would definitely take a bullet for.

But I wanted to make three questions. I wanted to ask you, everything I've read about girls and autism is that the sensory issues are so much stronger. And is that what you were talking about with the birthday song and that she can't handle all that emotion and attention towards her? Is that the sensory piece, because I think I've ready about

girls that the pronounced piece is sensory.

Dr. Pelphrey: That's the way I interpret it. The reason she doesn't like that is the feeling of all eyes on her, and the overwhelming -- she's just a -- it's hard for her to articulate it, but she's afraid of the song. I think, not to be too Freudian about it, but I think what happened was her first birthday we tried to throw a huge party and have every member of the family and every friend on the planet come over because we were so excited. And we kind of forced her into this social environment without really knowing about her vulnerabilities yet, and it overwhelmed her. And I don't think she remembers it as something that overwhelmed it, but just never -- you know, when the context happens again, she's terrified.

Speaker: And just two more quick questions. Where do you see OCD coming into this interplay? And then if you want to just add the last question is, so my son scripts also all day long videos, and it is the hardest part about play dates and other things. I've been told to try Namenda. I was also wondering if you have advice about interventions,

both pharmacological and non-pharmacological, about the scripting. And Temple Grandon's mom said she only let her script or stem for 20 minutes.

Dr. Pelphrey: To treat the scripting?

Speaker: Yes.

Dr. Pelphrey: I'm of two minds about this. Yes, most effective story. I'm of two minds, and actually Francis' mom and I disagree very strongly about this. She definitely wants -- she's a teacher and definitely wants to treat the scripting, end it, stop it. I grew up with a Vygotskian theorist back in college, and so I was very interested in how you take scripts from the outside world and narrative and internalize it so that you can understand your external world, and that's a normative development process. It's a stage and language development. It's what has been argued from a social and cultural point of view as something that's unique to humans being able to do that, and informing your world as a result of it. And so, I have a little girl who does that. She doesn't know that it's embarrassing, and maybe she doesn't care that it's inappropriate to do that out

loud. But if she were three we would be cheering her on. It would be called pretend play. And if we were Vygotsky, we'd realize that every time a person learns something new -- try programming a complex VCR for the first time -- all of the talking you do to yourself out loud as opposed to internal.

So I think a lot of it may well be using those narrative devices to figure out the world. So, for example, *Grease*. What an ancient story. You know, that has just about everything in it -- families, arguing, gangs, interactions, geopolitics, love, Romeo, Juliet. I mean, how many times has that story been told? And how many of us use rich stories and narrative to understand the world all the time? I mean, most religions have a story that you use to understand the world. Why do we call it "scripting" or give it a negative connotation if it's being used in a functional way to try to understand the world? I don't mean functional way in terms of looking normal, you know. I mean if it's working for them. And so, I promised her I wouldn't tell this story, so I'm not going to.

Speaker: Do you want to address Namenda and OCD?

Dr. Pelphrey: Oh, yes, OCD. You mean in Francis' particular case?

Speaker: Both my kids seem to have OCD as a big part of their personalities, and I was just wondering how that intersects with autism.

Dr. Pelphrey: Oh, it absolutely does. Genetically, brain systems wise, in every way scientifically, I can tell you it interacts. We tend to call those types of behaviors in the context of autism "autism," part of autism, but in isolation they could probably meet diagnostic criteria for OCD. I don't know how helpful that is, you know. It's sort of, well, okay, they have two disorders instead of one. But the underlying mechanisms is what I want to focus on.

And, you know, if they're different in autism versus pure OCD that would interest me. But otherwise, we approach them with the same analytic strategy and the same intervention strategy.

Speaker: And lastly, Namenda.

Dr. Pelphrey: Lastly what?

Speaker: Namenda, the drug for Alzheimer's that they're now using for kids with autism.

Dr. Pelphrey: I actually don't know anything about it other than what I've read in the press, so I can't really comment on it.

Speaker: Well, thank you so much. This has been wonderful. Thank you.

Dr. Insel: And with that, let's thank Kevin again.

[Applause.]

[Whereupon, the meeting concluded.]