

How Does the Autistic Brain Work?

PORTIA IVERSON: Tito is a very empathetic person, and he really realizes, he's met a lot of other children with autism and he really knows that by being a very special patient who can tell us about what being autistic is like, that this will lead to helping a lot of other people.

SHOW OPEN

ROBERT KUHN: Tito we appreciate having you here, we'd like to talk about how people study other people. How do you feel when scientists ask you questions and want to see how your brain works?

TITO WRITES ON PAD

SOMA: I get flattered.

LAUGHTER

PORTIA IVERSON: I have to tell you also Tito is a very empathetic person, and he really realizes, he's met a lot of other children with autism and he really knows that by being a very special patient who can tell us about what being autistic is like, that this will lead to helping a lot of other people.

ROBERT KUHN: You've studied Tito, Eric? What are the primary characteristics of autism?

ERIC COURCHESNE: Poor speech and language, particularly in the youngest child, two years old, sometimes an absence of speech and language altogether. Poor social communication skills, a disinterest in interacting with other people, the willingness to just stand up and walk away when people are talking with you, ritualistic and repetitive behavior. So they may be body mannerisms like flapping the hands or twiddling the fingers, or rocking and twiddling strings. Or they may be obsessive interests, interests in maps, for instance, just looking at maps for no particular reasons.

PORTIA IVERSON: One thing that was very interesting to me and Tito, I know I've asked you this, and Tito usually says, "I've told you that before," but I know the answer to this, but I think it's very interesting why you flap your hands and rock, would you mind telling people and how you experience your body and so on?

TITO WRITES

PORTIA IVERSON: I just need to find my position in space.

TERRY SEJNOWSKI: Hm, interesting, exploring space.

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ROBERT KUHN: How does rocking help you find your position in space, Tito?

TITO WRITES ON PAD

SOMA: I forget that I have a body and it reminds me of having one.

TERRY SEJNOWSKI: Well, you know, our brain is built to actively explore the world, and I think that what may be happening here, this is speculating, is that if you don't have that anchor in your body, you have to continually remind yourself, "I'm here, I'm here," and by moving back and forth, you can do that.

ROBERT KUHN: Well, also your kinesthetic sense of where your arms are and your legs [OVERLAPPING] at all times, we know that, we close our eyes, we know where our hands are, our legs are. But he may not know any of those things.

ERIC COURCHESNE: I think what it is, it's as if each of the senses are coming in separately and never connect up with each other.

PORTIA IVERSON: That's what he's describing.

ERIC COURCHESNE: Yeah, right, and that there's a lot of noise in that, and a lot of variability, and he has no way of, of, of keeping them focused consciously.

ERIN SCHUMAN: So he increases his sample rate by moving through the environment to increase the amount of sampling that he gets.

ERIC COURCHESNE: And to make at least one stimulus stronger.

ROBERT KUHN: Tito everybody at this table is a writer, has written different kinds of things, you write poetry.

TITO CONTINUES TYPING

SOMA: I write my experience. I do not have to wait long, because he just he doesn't sit to think, it's as if it is already precomposed, he just gets up in the morning after finishing whatever his necessary things and then he just writes them as speech.

TERRY SEJNOWSKI: Really, that's remarkable, so this is almost as if it was composed while he was asleep.

SOMA: It's just pre-thought.

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TERRY SEJNOWSKI: The poems that he has seem to occur to him in the morning. Now, why is that? This is something that I think all of us have experienced, we are struggling with a problem and we can't get the answer, we go to sleep, wake up in the morning and suddenly it's a lot clearer. We either have the answer or we know how to get to the answer, and maybe there's something going on during the period of sleep and we know a lot of activity is occurring in the brain, it's quite different from the activity that occurs when we are awake, but maybe this is the period during which not only memories are consolidated but new ways of integrating together information you have will be developed.

ROBERT KUHN: Does he read?

SOMA: Yes, he never used to read, but then again like I found that he can pinpoint even on a newspaper, but that I did not call reading, I do the proper reading like with him, line by line.

ROBERT KUHN: So you read to him.

SOMA: I usually read.

ERIN SCHUMAN: Do you read poetry to him?

SOMA: A lot.

ROBERT KUHN: Have you done that since he's been a small child?

SOMA: Every day.

ROBERT KUHN: Do you see any correspondence between the poetry you've read over the years and what he writes, thematically, or style?

SOMA: Some things affect him, like while he was reading that the book called *Alchemist*. So after, after that he heard the whole book and then he wrote *The Mind Tree*. So it's in that book, he gets inspiration like that.

TERRY SEJNOWSKI: Oh yeah, I have the, is this. It's a different one.

SOMA: No, no, no, it's, it's different one, it's just *This And That*, "like there was a little desire and a little hopelessness a little looking ahead and a little looking back, a little sunshine and a little shade, a little of this and a little of that." Everything goes like that with a little of this and a little of that.

TERRY SEJNOWSKI: And each time it's in the morning?

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SOMA: Every time, like one day he wrote everything about orange, he got so obsessed with that, here he starts orange. “On a hidden back with orange sparks on little dust grains, orange on this and that. Orange on hidden wild flower behind a hidden rock, gathering time with ages to stay, green with gathering moss. Orange on a peeping beam, through the canopy green.”

ERIN SCHUMAN: So he is able to see orange and all these different things, so he is able to sort of synthesize things in a way in his poetry.

SOMA: Orange and blues and blacks.

PORTIA IVERSON: If you read his poetry you’ll actually notice that there’s very little imagery, surprisingly little. And in poetry you often see a lot of visual descriptives, and in fact he has a mentor, Stephen Berke, the poet, is his mentor now, in Philadelphia and they correspond by email. And Stephen has been advising him to try to incorporate more visual component to his poetry, which is very hard.

ERIC COURCHESNE: I think that would be really hard for him.

ROBERT KUHN: Then how does he put it down on paper, does he write it?

SOMA: Yes he usually writes it and then he types it. He sometimes edits it.

ROBERT KUHN: On the computer?

SOMA: Yes.

TERRY SEJNOWSKI: How did he start using the computer? Was that something natural for him?

SOMA: No, I gave him this computer a year before last, and after that he started, but he’s pretty fast in picking things up, he corrects himself, backspace and all those things, he opens his files and all those.

PORTIA IVERSON: Tito has some very interesting descriptions in his book in his writing about early sensory experience. Tito can you tell us something about, remember when you were talking about when you were a really little boy and it was so difficult to understand the environment?

TITO WRITES

PORTIA IVERSON: He does one description where he says, he’s looking out the window at a cloud, and somebody says the word “banana,” excuse me if that wasn’t the

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exact word, but I think it was banana, and they go together forever. So he starts just listening and not looking, or just looking and not listening. And then at a certain point it seems like these sensory systems diverged and kind of came apart instead of the average developing kid is further integrating these systems over time developmentally.

ERIC COURCHESNE: Sensory instances, the cloud and the banana collide, interact, and become formed as a single memory, and that's really common in autism. And a major question is, why does that happen? One possibility is that you have a proliferation of connectivity in cerebral cortex early on that is driven almost randomly, allowing interconnections that ordinarily wouldn't be there.

PORTIA IVERSON: Another idea which I've been talking to Mike Merzenich about up at UCSF about is the idea of a kind of early over selectivity coming on too early, because if you can't make sense of your universe because everything is going together, and then you use selective attention to focus on one sense modality in order to just simply know this is a glass, this isn't banana glass, then what would happen is he would start probably to lay in circuits very early that would now become the underpinnings of a whole nother learned behaviors and other learned behaviors that would network in on top of that.

ERIN SCHUMAN: But one of the thing that I think is interesting that reveals is that he can form associations, but for any other animal you would need many trials, you could get someone to make the association between cloud and banana, but for a normal individual it would take many, many trials to form that association, so he has a hypersensitive ability.

ROBERT KUHN: Tito, how do you see the door?

TITO TYPES

SOMA: The shapes come first...

ROBERT KUHN: The shapes come first, and then the color.

TERRY SEJNOWSKI: And it comes over time, you have to put the pieces together, that's something that we take for granted.

ERIC COURCHESNE: So you're saying the larger an object is, the more difficult it is for you to perceive it. And you perceive it in parts or fragments, shape and then color.

TITO WRITES ON PAD

SOMA: Only after I see the door. I see the room only after I see the door.

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TERRY SEJNOWSKI: Yeah, that's almost poetical. It illustrates something that we're beginning to understand about our own perception, which is normally you see the whole before you see the parts, and it looks like it's the opposite for Tito. One of the problems that Tito has is a problem with putting the world together. Normally we don't think about the fact that we're, we can see someone and listen to them and touch things and it all comes together in our brain almost automatically. But in some cases, and specifically with Tito, those things are disconnected and it's not easy to put them together, and the world must be very frightening when things are coming at you unexpectedly and things don't connect. I think we can learn a lot about how the brain normally works, things that aren't apparent to us because it works so well when we see breakdowns like this. We don't understand how difficult that is to put together all the different pieces of the world and, and make it a unified whole.

ERIN SCHUMAN: I think one of the things that's interesting about Tito's case, and rather hopeful, is that it's clear that working together with his mother and the team that has worked with him, there's a lot of information there that we just didn't know how to get out, and with the computer and the voice synthesizer it's clear that he knows a lot more than if, the conventional methods of probing what an individual knows would reveal, which suggest the possibility that there may be other cases like Tito where there is a lot of information and a lot of synthesis that just, where there's no output.

SOMA: I can see a point... It can become bigger than the door, just a point, and he can just concentrate on that point and the other things get unnoticed.

PORTIA IVERSON: We were looking at a door one day and as he described here he said, "I see the shape, I see the color, I see the position." I said, "what if I close it," he said, "I may have to start all over again." And a few weeks later I asked him, in the average everyday world we're confronted by thousands of kind of images in any given second, some moving, there's depth, "how do you see all this?" And he said, "one by one."

ERIC COURCHESNE: It's almost like they focus in like a spotlight on just a piece of the world around them, and in order to put it together they have to shift that around and around and piece it slowly together. It takes over his consciousness.

TERRY SEJNOWSKI: Maybe that indicates an overactive form of attention, normally we can tune out other sounds and, and events and focus on one object, but usually we're continuing to be aware of the rest of the world, it's just that we are focusing and if you can do that extremely well, you can imagine that there's nothing else out there except that object and it becomes your whole world.

ERIC COURCHESNE: Not just overactive but almost active in a way that's out of his control, so that he is not able to easily and smoothly adjust his scope of attention to take

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in the whole scene, let alone a part of a scene, so that he is reduced to just a single feature of a scene.

ROBERT KUHN: What are some of the modern theories on how attention works and how we bind things together?

TERRY SEJNOWSKI: It's really the prefrontal cortex, the part in the front of the brain that allows your mind to selectively attend to particular senses and particular features, and in fact switch between different objects, and that's something that, again we take for granted, we don't think twice about switching between a discussion with you or with Eric and back and forth very rapidly, but it's something that is very difficult for Tito.

ERIC COURCHESNE: In fact not only brain stem structures but also frontal cortex structures and structures in parietal areas as well as the structure back here the cerebellum, another cortex, all these structures are involved in the dynamic regulation of attention and allow the rapid, smooth and effective shifting of attention from one sensory percept, for instance, color and shape to another, or between sensory modalities between vision and audition. And what we and others have found is that autistic individuals have a great deal of trouble doing this, and they tend to get stuck on one thing as if their attention got locked in and was out of their control. So apparently systems that allow the smooth modulation are not effective.

ROBERT KUHN: What I'd like to do now is stick with the cerebral cortex or cerebella cortex and discuss another area of functioning that we discussed very significantly in our lives, the nature of sleep, which has been shown to be associated with memory consolidation, and so let's focus on memory and touch on sleep and see how the brain works. How does memory work?

ERIN SCHUMAN: How does an organism store information about its environment, right, that's essentially what a memory is. It's stored at the connection between neurons at the synapse and is likely mediated by changes in the strength of communication, so the impact that one cell can have on the other cell.

ROBERT KUHN: That's done through chemicals that pass back and forth.

ERIN SCHUMAN: Right, so the first cell releases a neurotransmitter that the second cell detects, and it changes that chemical signal into an electrical signal. So, information can be stored by changing the strength of that electrical signal. And then, once you get past the synapse you get to the cell, and the cell has to integrate the information that it's receiving from all of the cells that are talking to it. And, so in the hippocampus all of those synapses come into a single cell. In the '50s one patient HM had both of his hippocampi removed, so the brain has two halves, so each person has two hippocampi. And in HM what was noticed is that he had profound amnesia following the surgery so he

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was incapable of forming new memories, so that was one of the first clues that the hippocampus is important for memory formation. And animal studies that have been done since then have, have basically borne that out, that for certain kinds of memories, animals that lack a hippocampus cannot form those memories.

ROBERT KUHN: How about long-term memory?

TERRY SEJNOWSKI: We think that semantic memory, memory that we have knowledge about the world resides in the cerebral cortex, but there is a period during which you need to have a dialogue between the hippocampus that Erin was focusing on and the cerebral cortex, back and forth, for that memory to be consolidated in the cortex.

PORTIA IVERSON: Tito is telling us that, “I have that better,” meaning that he has better memory than average.

TERRY SEJNOWSKI: And that could well be, if you can really focus your attention on something, you can really encode that in a way that will be there for a long time, and attention is, is clearly directed by a lot of these neuromodulatory systems, like I say, the choline and serotonin. If you could really focus the way Tito does I think you could make that very strong association.

PORTIA IVERSON: This is, this is really relevant to what you're saying and we've tested this a lot with people. READS FROM PAD He says, “I have that better,” meaning memory long term, “but I forgot my breakfast menu,” and he really means it. I mean, if I were to ask Tito, well “give me examples of breakfast food,” he'd probably give, I guess, a lot longer list than us, but if I said, “what did you have for breakfast,” he may absolutely not be able to tell us because of the way the information is stored, I think. He needs a handle on it, he needs to get a hold of a tag, like a computer, like artificial intelligence, like you couldn't ask a computer, “what is this,” or “what did you do an hour ago,” you must give it some commands, and that's a lot how Tito's brain works.

ROBERT KUHN: Let's spend a few minutes talking about the where autism occurs, we know the brain works every place from the neurons, the synapse between those neurons to neural networks which are small associations, going to get the brain structures and brain systems. On what level can autism be occurring at?

TERRY SEJNOWSKI: Why not all of them?

ERIN SCHUMAN: To the extent that these things, that autism has an underlying genetic or biological mechanism, it can be a quite fundamental mutation. So I think one of the things that's perhaps not intuitive is that the underlying biological mechanisms for these very complicated behavioral disorders can be something very simple about the way a synapse works.

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ROBERT KUHN: But it doesn't have to be there, it can be a gene connectivity issue, it can be a synaptic _____ as primary cause. Everything is affected, but what's the primary cause?

ERIC COURCHESNE: We do know that, that a gene factors, genetic factors must be very large in this disorder because identical twins one of whom has autism, have, there's a 90 percent chance that the second will have autism, whereas fraternal twins, in which you have two individuals that are non genetically identical to each other...

ROBERT KUHN: Just like brothers and sisters.

ERIC COURCHESNE: There's a 0 to 50 (or 15?) percent chance that the second will have autism, so this disparity between the concordance of autism in the twin, the identical twin pair vs. the discordance for autism in fraternal twin pair speak strongly to genetics. And most people believe that there's probably two to four or five different genes that are involved in this disorder, and so it's very hard to really pin down which gene might be, and so a single gene might manifest itself throughout the brain.

TERRY SEJNOWSKI: But now here's a challenge, so you mentioned that identical twins have a concordance of 90 percent, so that means if one of them has autism, it's probably 90 percent that the other one will also have autism. But it also means there's a 10 percent probability that the other will not have autism, and what is missing here, in other words, why is it that with the same genes you can start out and one has autism and the other doesn't, I think that's a mystery.

ERIC COURCHESNE: We know of course that, that one or two genes don't make a person. We have tens of thousands of genes that are the blueprint for our bodies, for the biology of our bodies. And so it's probably those other genes that are non-affectant that may impact.

TERRY SEJNOWSKI: What about the environment?

ERIN SCHUMAN: There's even a whimsical nature to genes, I mean some of the things we've learned from knockout studies where a single gene is mutated in a mouse, in some cases in a litter you'll find 30 percent of the mice lack a kidney, and they all, they're genetically identical, so there is a whimsical nature to the way genes play out their program in the development of the organism that isn't as hard wired as we would like to think.

TERRY SEJNOWSKI: Some of that whimsy occurs in the womb, so it turns out that the environment that the fetus develops in has a major impact on how the brain develops.

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ROBERT KUHN: Let's talk about the search for a cure for autism, I mean not just helping with symptoms, but a real cure. How do you see science working to cure autism and other similar kinds of diseases?

ERIC COURCHESNE: Well I think that science proceeds by exploring possible biological mechanisms that lead to the phenomena of autism, both its behavioral and its brain phenomena. And some of these clues are going to lead us to possible biological interventions that can be very effective. The most remarkable story of this sort is a disorder called PKU, PKU was a disorder, and is a disorder in which, if not treated, the child becomes mentally retarded, from, from birth, the child's chemistry is no longer protected by mother's body, the child's chemistry is not able to control the use of certain chemicals, an amino acid, phenylalanine, that's commonly available in foods, and as a result, toxic levels of this amino acid build up and produce brain damage. But knowing that allows a very simple and effective treatment, after birth a child that has the gene mutation, PAH that prevents the normal metabolism of this amino acid, such a child is put on a diet that has low quantities of this amino acid.

ROBERT KUHN: That's a terrific story.

ERIC COURCHESNE: And what happens, normal brain development follows, something similar might occur with other developmental disorders if we knew.

PORTIA IVERSON: There's a subset of children with PKU who have somewhat autistic like symptoms, I only say that to demonstrate that a simple enzyme missing can cause a huge spectrum of complicated behavioral symptoms.

TERRY SEJNOWSKI: Well I think that the key here is having knowledge, in other words, knowledge that there's a particular amino acid and a particular gene that's wrong. We might be able to, if we knew what genes were involved, we might be able to catch them really, really early, before they even start manifesting themselves.

ERIC COURCHESNE: And in autism actually, there are two very interesting facts that may have something to do with each other that may eventually lead to this kind of intervention. One is the finding that, at birth the brain of the autistic individual is normal in size, but by two years it's grown to be far larger than normal. So the question is, what's, causing that?

ROBERT KUHN: Some kind of stress.

ERIC COURCHESNE: Well it turns out that one scientist at NIH has described there being elevated brain growth factors at birth in children who later become autistic, so these brain growth regulators seem to be in too great abundance. And the interesting point is, that for the first time molecular factors that may influence brain outcome have been identified at birth and blood samples from autistic individuals. So that gives one

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hope that the pathways that lead to that and out of that that point may be investigated and perhaps modified, producing a far better outcome.

ROBERT KUHN: Do any of you have concerns about the future in brain research in terms of how information we're learning can be misapplied?

TERRY SEJNOWSKI: Tough question. The danger is that the knowledge that we're going to have very soon with the techniques that we have developed for imaging and seeing into people's brain could be used someday perhaps in a society different from ours, to control human beings.

ERIC COURCHESNE: Well, certainly just about every human technological development at some point or another by someone has been used for ill.

TERRY SEJNOWSKI: That's always the concern.

ERIN SCHUMAN: Science at its core has a sort of blind, knowledge is good, you know, doing the experiment shouldn't be questioned because it's the sort of blind search for the truth, right?

ERIC COURCHESNE: I think there's no doubt that this will be true for any other knowledge that might be gleaned from brain science, by brain science. But at the same time technology has brought tremendous good for people. So it's that balance between the two.

SOMA: "I think that it will lead to the better kinds of treatment.

ROBERT KUHN: Tito, thank you very much.

PORTIA IVERSON: Can I just make one comment that I think is kind of important? The diverse approaches we need to go at a disease like autism, I think you can see, range from genetics, to a person like Tito who can shed light on it, to a person like his mother who has made major discoveries in how to teach children with autism how to communicate.