Transcript Details
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ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

Uncovering the Brain Bases and Genetic Causes of Autism

ReachMD:
Brain studies are one of the critical areas that researchers are looking for the causes and possible cures for autism spectrum disorder. A new study published in the New England Journal of Medicine provides physical evidence that autism spectrum disorder has roots in prenatal development. You're listening to ReachMD. I'm Paul Rokuskie your host and with me today is Dr. Eric Courchesne, Professor, Department of Neurosciences at the University of California, San Diego. Welcome Dr. Courchesne.

Dr. Eric Courchesne:
Hello. It's good to be here. Thank you very much for inviting me.

ReachMD:
So if you can tell us a little bit about your professional background?

Dr. Eric Courchesne:
I'm a neuroscientist and the reason I'm a neuroscientist is because I personally experienced a neurological disorder. When I was 4 years old I was in the last polio epidemic in the United States. I was about 4 years old at the time and the results of the polio were that I couldn't stand or walk. Wow. That leaves a big impact and impression on a young child so from the very beginning I knew I wanted to study neurological disorders that began at very early ages to help children who have them. Help them either recover from them or come up with methodologies that might prevent disorders like polio.

When I was in my ‘20s I met a young autistic teenager. He was just a super person. His parents were a doctor and a nurse. It was pretty clear that he had a neurological problem but at the time polio was overlooked. People weren't interested in polio. It was considered to be a rare disorder and not necessarily caused neurologically so I dove in. I decided this would be a disorder I would tackle and do nothing else.

ReachMD:
That was polio that you wanted to try and conquer or autism?

Dr. Eric Courchesne:
You would think it would be polio. You would think I would have been interested in studying post polio syndrome but you know I already had polio and there were vaccines for polio and that prevented polio but here was a family that had a child with autism. It was pretty clear that no one knew what caused it, when it began and what could be done about it. That was something that I felt really deeply needed to be done.

I'd learned from my mother that you know it's really important when children have disabilities to do the very most you can to help those children so there was autism unstudied. I don't think there was a single neuroscientist in the world studying autism at the time that I began. Autism became my lifelong professional passion.

ReachMD:
Can you tell me about the research that you and your team have been working on?

Dr. Eric Courchesne:
About a decade and a half ago, our research identified a really surprising overgrowth of the brain that occurred very early in the first two years of life in a substantial subset of individuals with autism. This early brain overgrowth in autism suggested to us the possibility that it was caused by an excess number of brain cells. A pretty simple idea but very difficult to test.

In order to test it we had to get autism brain tissue so it was necessary to directly do cell counts. It took _____ (3:25) on the order of about seven years to identify and collect and then section the samples of individuals who had passed away with either autism or who were controls. We wanted to study really young individuals. Most of the individuals had passed away through drowning or other accidents. We set about a very careful winded study in order to determine whether there were in fact an excess number of brain cells.

The part of the brain we were most interested in was the frontal cortex or the frontal lobes. The frontal lobes are at the front part of the brain right under your hand. If you put your hand right on your forehead it's the part of the cortex that is really important for high-order human social, cognitive, language and emotion functions. It's the part of the brain that has shown really remarkable changes across evolution. It's grown very large in humans. It's role is a role that mediates the same functions that are abnormal in autism, namely social communication and high-order cognition. We reasoned that was a good place to start.

We counted brain cells in that region of the brain and we were shocked to find that there was not just a greater number of brain cells but a very much greater number of brain cells in prefrontal cortex in the brain of really young autistic individuals as compared to controls. In fact, overall, there were 67 percent more brain cells than controls, which is a gigantic increase. In the youngest individuals, the increase was almost 100 percent, more than twice as many brain cells.

ReachMD:
What is the methodology of your study?

Dr. Eric Courchesne:
The method is stereology and the procedure is to serially section through the entirety of frontal cortex and then to identify the regions to be counted and then do an unbiased random counting where you essentially place your counter in random locations so you're not deliberately controlling where it goes. Then you systematically randomly do counts and you're looking at sections of the brain under a microscope and doing counts.

The methodology that we use is really important. We wanted this to be the strongest study possible so I identified one of the world's foremost experts on stereology. The person who literally wrote the book on stereology, Dr. Peter Mouton. He had never done research on autism before. He had no preconceptions. I didn't tell him what the study was about. I didn't tell him what the hypothesis was.

We also identified one of the world's foremost experts in frontal cortex anatomy and the same thing he knew everything there was to know about the regions of the frontal cortex and how to do cell counts and how to do boundaries of those regions. Once again, he didn't know what the purpose of the study was or what our hypothesis was.

We could have done all these studies ourselves but then you know sometimes bias enters in so what we did was a blinded design in which we coded all the samples and all the slides so that when they went to the stereologist and to the anatomist for delineation and counts, they were completely unable to tell which case was a control and which case was a patient. Furthermore, in the case of each of these individuals they didn't know what the purpose of the study was. It was really a very carefully winded and unbiased study of cell counts.

ReachMD:
If you're just joining us you're listening to ReachMD. I'm your host Paul Rokuskie and I'm speaking with Dr. Eric Courchesne, Professor Department of Neurosciences at the University of California San Diego.

We're talking about brain studies and their impact on autism spectrum disorder research.

Dr. Courchesne, we hear a lot about traumatic brain injury studies being conducted on the brains of soldiers, NFL athletes and individuals with Alzheimer's. How does your work with brain tissue mirror or differ from these other studies?

Dr. Eric Courchesne:
Some of those are similar and some are different. Some are qualitative and some are quantitative. Some are studies that are using a stereological method, so our first study of cell counts was a stereological study.

Our second study that was published in the New England Journal of Medicine this year was both quantitative as well as qualitative. That was quite an original study because we had found a large excess of brain cells. That suggested to us that autism begins in the second trimester because that's when brain cells are normally generated in the human frontal cortex. A large excess, 67 percent, points to a dysregulation of what's called cell cycle systems or systems that regulate cell cycle. These systems when they become dysregulated can produce not only a large number of brain cells but they might produce the wrong types of brain cells or they might produce brain cells that end up in the wrong location.

That would point then to a second affect, which would be a failure of the normal organization of cortex. That is the normal patterning of

where different types of brain cells form layers at the surface of the brain. Each layer does something different for the computational functions of the brain.

We reasoned if there were an excess number of brain cells, there might be a failure of the normal layering and there might be cells that end up being scattered or located in the wrong spot. We did a very unique study looking at specific cell types and layer types. We examined 11 autistic individuals who had passed away at young ages from ages 2 to about 14. We compared them to controls. What we found was that in the same regions with excess cells there were patches of focal disorganization of cortex. Near these patches of disorganization there were failures of the normal layering so you have a failure of the normal layering, you have a mismigration of cells that also points to the second and early third trimesters when brain cell production and cortex organization is performed.

ReachMD:
Are you seeing genetic or environmental factors in your research?

Dr. Eric Courchesne:
Our research points to the possibility of both and the research in the field points to the possibility of both. These two studies of ours are the first to look directly at brain tissue that categorically point to the second and third trimesters. Other groups have looked at genetic information and have done essentially what's called bioinformatics analyses. Taking into account the genes that seem to be mutated in rare cases of autism, they've asked the question of when those genes are important for brain development. In one recent study, the answer pointed to prefrontal cortex, as we have found and to the second and third trimesters, as we also found. That genetic study independently points to the same location and the same timeframe.

Recently, there have been animal model studies looking at transgenic animals and loss of function mutation animals and asked the question of whether the brain development in those animals that have autism relevant genes knocked out. That is there's a loss of function or a mutation of those genes. They've asked whether those genes produce some of the same anatomy that we have found and it turned out that they do.

At the same time, other researchers have looked at mouse models and asked the question of whether a different idea about the causes of autism might lead to the same anatomic features. The different causes that have been explored have been immune causes, specifically maternal immune activation during pregnancy, during the first or second trimesters. The question is whether some sort of immunological dysregulation at that time during fetal development might lead to early brain overgrowth and abnormalities of the formation of cortex. It turns out they do as well.

There could be more than one path to triggering this abnormal set of production of excess number of cells, abnormal organization of the brain, mismigration of brain cells so they end up in the wrong location and autistic symptoms.

One very recent study combined the two. A study took a gene that's not uncommonly found to be mutated in individuals with autism and asked in animals just how much overgrowth occurs and there's a small amount of overgrowth.

Then this research group from UCLA Lavelle asked well now if we add on a maternal immune challenge in the first trimester happens and the combination of the genetic defect plus the immune produces a whopping overgrowth.

Many people are now thinking that autism does in fact involve in many cases a combination of genetic and non-genetic maternal immune dysfunction.

ReachMD:
Dr. Courchesne, how does the launch of Autism BrainNet new donor registration website takesbrain.org help with your future research?

Dr. Eric Courchesne:
Our research points to really important possible directions leading to understanding of the underlying causes and triggers of autism. To fully understand this is going to require more brain tissue, brain tissue from autistic individuals as well as control individuals. At the present time in fact, there is very little brain tissue, too little to address the really extremely important questions that now come up as a result of these several studies that have been done by other laboratories and our laboratories. Many people think well of course you know what's really important is to collect more autistic brain tissue for research and what's going to turn out to be the case I suppose. I predict that it's going to be the young cases that will be most informative because there's an ongoing change in the brain in autism with ages.

Autism is a brain disorder and without knowing the details of the brain disorder we won't be able to get as far as needed to understanding causes and potential treatments. The most important path is understanding the biology at the level of genes and molecules and brain cells and synapses and connections and that can only be done by studying brain tissue. We hope this initiative is very successful and leads to enriched studies of autism.

ReachMD:
Thank you very much Dr. Courchesne for your time today.

Dr. Eric Courchesne:
Your welcome. Thanks very much for your questions. It was good talking with you.

ReachMD:
Many thanks again to my guest, Dr. Eric Courchesne, Professor at the Department of Neurosciences at the University of California San Diego. We've been discussing autism spectrum disorder. Be sure to visit our website at ReachMD.com featuring podcasts of this and other series. I've been your host, Paul Rokuskie, and thank you for listening