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Unravelling the mystery of autism

One of Canada's lead scientists in the Autism Genome Project explains how this massive international effort is zeroing in on the genes that cause autism, and why we are closer than ever before to eradicating it.

Dr. Peter Szatmari, Director of the Offord Centre for Child Studies, made headlines recently for his role as one of the lead scientists in what has become the largest genome scan ever attempted in autism research.

He and Stephen Scherer of the Hospital for Sick Children are part of an international team that has zeroed in on two previously overlooked areas of the human genome – a gene called Neurexin 1 on Chromosome 2 and a region of Chromosome 11 that houses genes involved in the brain chemical glutamate, an important neurotransmitter. We interviewed him to learn more about how these may contribute to a child's chances of having autism, and what this latest discovery means for children and their families.

Q. You've been diagnosing children with Autism Spectrum Disorders (ASD) for more than 20 years, and you've seen a lot of developments take place that have increased our understanding of this complex disorder. How significant are these latest findings?

A. Potentially, it's very significant. If we want to come up with a biological marker for diagnosis and a biomedical treatment that addresses the fundamental deficits that individuals with autism have, then we have to understand the causal chain that goes from gene to disorder. What we need now is for other researchers to replicate our work, come up with the same findings, and start to build that causal chain.

Q. More than 1,300 families participated in this study. How important was it to have a sample of this magnitude?

A. It's true ours is the largest genome scan ever attempted in autism research, and one of the largest for any human disease. With such a large sample, it's less likely that we would have come up with these findings by chance alone. So we can have a lot more confidence in our findings.

It also allowed us to identify more specific pathways for sub-types of the disorder – affected females, for instance, or those with just language problems. When you have a really large pie, you can divide it up and still get large samples. This allows us to gain a better understanding of how individuals come to be affected through different pathways, so that we can ultimately do a better job of diagnosing ASD and treating individuals based on these differences.

Q. In announcing your findings, you said: "Not only have we found which haystack the needle is in, we now know where in the haystack that needle is located." What did you mean by this?

A. Every person has 23 chromosomal pairs containing a total of roughly 30,000-40,000 genes. We know that there are upwards of 10 to 15 genes involved in autism. Where are we going to look? These findings not only tell us which chromosomes (or haystacks, if you will) are involved, but where on the chromosome (or in the haystack) the genes might be. If our hypothesis about glutamate turns out to be true, it's the closest we have come to date to understanding the biochemical pathway that leads to autism.

Q. Scientists have long suspected that individuals with autism have brains that are "wired" differently. How does the implication of Neurexin 1 fit with that knowledge?

A. We have known that there are many different ways that the brains of autistic individuals might be affected, but we haven't known which neurotransmitters might be involved. This gives us information that is much more specific than we have had to date. It identifies a specific neurotransmitter system, the same one that has also been implicated in epilepsy. There are medications already available that affect this specific neurotransmitter system and that are being used now to treat epilepsy. By zeroing in on this neurotransmitter system, it brings us that much closer to a diagnostic test and biomedical treatments that can be used effectively on autism.

Q. You were quoted in the media as saying, "I don't think it's inconceivable that we're going to be able to prevent autism down the road." What did you mean by this?

A. If this leads us to better biomedical markers, we will be able to make a diagnosis of autism earlier. With earlier diagnosis, it's conceivable that we could put in place interventions prior to full development of the disorder, which is somewhere between 18 and 24 months of age. We may even be able to intervene before the end of the first year of life, and to me that sounds like prevention.

Q. How close are we to having a DNA test that would diagnose autism in babies or even before a baby is born? How will this knowledge change the quality of life for these children and families?

A. The first step, as I said before, is to have someone replicate our finding and agree with it. The second step is to know how many cases of autism this finding accounts for. Then we need to see if developing a

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Anxiety, autism or temperament? Making sense of sensory problems

by Nancy Pollock

Temple Grandin, who overcame autism to earn a Ph.D. in animal science from the University of Illinois, once compared her hearing to "having a sound amplifier set on maximum loudness".

"Sudden loud noises hurt my ears," she said, "like a dentist's drill hitting a nerve."

Temple is not unique among individuals with Autism Spectrum Disorders (ASD). Parents of children with ASD often say their children are not able to tolerate certain sounds. They often object to having their teeth cleaned or their hair brushed. They may be irritated by clothing tags or certain fabrics. They will often spit out foods that are crunchy or mushy.

Research has shown that children with ASD, Attention Deficit Hyperactivity Disorder (ADHD) and Asperger syndrome do seem to have different responses to sensory inputs than typically developing children. A recent study[1] has shown that some typically developing children also have auditory and tactile sensitivities. In this study, girls who have a fearful temperament were more prone to these sensitivities. Their temperament makes them more prone to being frightened of new experiences or anxious about things that don't bother most people.

We know that children with ASD are very prone to anxiety, so it may be that sensitivities to sound and touch are related more to having an anxiety disorder than they are to having an autistic disorder.

At this point we don't know if these sensitivities are related to a developmental problem, to anxiety, to the child's temperament or to some combination of these factors. What we do know is that the problems are real and can make daily life very difficult for families.

So, what to do about it? One intervention that is widely used is called Sensory Integration Therapy (SIT). Originally described by Jean Ayres[2], an occupational therapist, SIT is designed to help children integrate sensations they receive from movement, touch and body position, as well as vision, taste, smell, and hearing and to use that information to attend and listen, to move efficiently, and to learn new skills. Therapy can involve swinging in a net, rolling on large balls, resistance exercises, brushing the skin, and deep pressure touch.

Despite strong support from parents and some therapists, current evidence suggests that SIT is no more effective than other therapies, such as academic tutoring and perceptual motor therapy, which uses integrated movement to improve motor skills and visual perception problems.

Fortunately, there are things that families can do. A number of books provide practical ideas about how to address children's sensory challenges. Many occupational therapists have expertise in analyzing children's patterns of sensory processing and guiding parents and teachers in making changes to tasks, environments and routines that can help children cope more effectively with their sensory issues. Small changes in such things as texture, temperature, timing, pace, color, noise or light levels can make a huge difference in a child's behavior or performance and make daily routines a lot easier for families.

[1] Goldsmith HH, Van Hulle CA, Arneson CL, Schreiber JE, Gernsbacher MA. A population-based twin study of parentally reported tactile and auditory defensiveness in young children. Journal of Abnormal Child Psychology 2006, 34(3): 393-407.

[2] Ayres, A. J. (1972). Sensory integration and learning disorders. Los Angeles, CA: Western Psychological Services.

Ayres, A. J. (1989). Sensory integration and praxis test. Los Angeles, CA: Western Psychological Services.

Nancy Pollock's recommended reading list for parents of children with sensory challenges:

Sensational Kids: Hope and Help for Children with Sensory Processing Disorder by Lucy Jane Miller and Doris A. Fuller (2006). Published by Penguin Putnam Inc., New York, NY.

The Out-of-Sync Child: Recognizing and Coping with Sensory Processing Disorder by Carol Stock Kranowitz and Lucy Jane Miller (2006). Published by Penguin Putnam Inc., New York, NY.

Raising a Sensory Smart Child: The Definitive Handbook to Helping Your Child with Sensory Integration Issues by Lindsey Biel and Nancy Peske (2005). Published by Penguin, New York, NY.

The Sensory-Sensitive Child: Practical Solutions for Out-of-Bounds Behavior by Karen A. Smith and Karen R. Gouze (2005). Published by Harper Collins, New York, NY.

Too Loud, Too Bright, Too Fast, Too Tight: What to Do if You are Sensory Defensive in an Overstimulating World by Sharon Heller (2003). Published by Harper Collins, New York, NY.

The Out-of-Sync Child has Fun by Carol Stock Kranowitz and T.J. Wylie (2003). Published by Penguin Putnam Inc., New York, NY.

Asperger Syndrome and Sensory Issues: Practical Solutions for Making Sense of the World by Brenda Smith Myles, Katherine Tapscott Cook, Nancy E. Miller, and Louann Rinner (2002). Published by Autism Asperger Publishing Co., Shawnee Mission, Kansas.

Trying a new therapy? Heed these words of advice

Nancy Pollock advises parents who are contemplating Sensory Integration Therapy (SIT) or any other unproven therapy or program to:

- Find out all you can about the treatment, especially how much it costs and whether or not it has the potential to cause harm.
- Think of the therapy as a trial and make sure that you are clear about what improvements you expect to see and how they are going to be assessed and measured.
- Set a time frame up front for measuring change. How many intervention sessions will my child need before I will see change? How quickly will I know if this is working or not?
- Make careful observations of those behaviors you want to treat before you start, so that you can tell if real changes are taking place.
- Remember, time and money spent involving a child in one type of intervention is time and money not available for something else that may be beneficial. Make sure it is worth it!

Nancy Pollock is an occupational therapist involved with CanChild Centre for Childhood Disability Research at McMaster University.

Sleepless nights a special challenge for parents of children with autism

Trying to get your child to go to sleep and stay asleep is a situation every parent dreads, but for parents of children with autism spectrum disorders (ASD) it can be a nightmare.

Many children with ASD resist going to bed, stay awake for a long time after being put to bed, or wake often during the night, and no one yet knows why. There could be many reasons. They may be anxious about going to sleep. They may have problems settling down for bed. They may be overly aware of noises in the house or light in their bedroom, or their melatonin system (melatonin is a hormone that helps people sleep) may not be working properly.

Are sleep problems a symptom of other problems?

Many children with ASD have co-existing disorders such as anxiety, attention deficit/ hyperactivity disorder, or depression. Any of these conditions can affect a child's ability to sleep.

Older children who have trouble going to sleep may be experiencing anxiety that has persisted throughout the day. This can be related to expectations for them to participate in social interactions that they fear.

Can a good night's sleep reduce autism symptoms?

There is some good evidence that nighttime sleep problems and daytime behavior problems are linked, but not necessarily in a "chicken or egg" way. No one knows if the sleep problems are caused by the same brain chemical malfunction that influences repetitive or disruptive behaviours in children with ASD. In any case, researchers have found that improving sleep quality reduces the severity of the behavior symptoms in children with ASD. Some researchers have also found that reducing sleep disruption improves repetitive behaviors and improves social interaction.

How can parents help their child with sleep problems?

Maintaining routines and having consistent rules are very important for children with ASD. If reading a story to your child is part of their bedtime ritual, it's important to be consistent. If it's one story tonight, but two or three stories the next night, then no story at all, the child's anxiety can increase. As the child gets older, it may seem appropriate to stop the bedtime story. Keep in mind, though, that any changes in the child's routine need to be introduced slowly, and that sometimes routines are best kept because they work.

Some children insist that mom or dad lie down with them to help them get to sleep. Doing this will eventually result in the child being unable to go to sleep alone. And when the child wakes in the night, they will need a parent to help them go back to sleep. Parents often respond by allowing the child to sleep with them (co-sleeping). While this may seem a good solution, especially if there are safety concerns, it encourages repeated wakefulness instead of curing it.

Depending upon the child's developmental stage and the kind of sleep problems they have, behavioral interventions may be needed to promote sleep. So if the problem is severe, consult your pediatrician.

Lesley Hayhurst-France, a behavior therapist at McMaster Children's Hospital, suggests a few tips that can help:

- Provide visual schedules of bedtime routines to increase consistency and predictability.
- Provide visual rules about staying in one's room or bed at night and post them in the bedroom.
- Accompany routines and rules with social stories that can address the child's anxieties related to sleep.
- Rearrange the environment: Install a nightlight, darken the room, put the bed up against the wall, or use "white noise" (a soft sound that drowns out noise), such as turning on a fan.
- Use a sleeping bag or a body pillow to provide pressure or "replace" a parent lying down with the child.
- Layer the child's pyjamas or tuck them in snugly to reduce any tactile sensitivities.

Does melatonin work?

Melatonin is being widely used to treat children and teens with ASD, despite a lack of research on its use in children with autism. Recent studies have not found any serious side effects from using it but the studies have had short follow-up times. It also doesn't work in everybody. If you think you'd like to use it with your child or teen, make sure you buy it from a reliable source and consult your family doctor or pediatrician first.

A simple remedy

One of the simplest remedies may be just putting your child to bed later. In one study, researchers found no difference in sleep duration or sleep quality between children with Asperger syndrome or high functioning autism (HFA) and typically developing children of the same age. However, the children with Asperger's and HFA did go to bed earlier and took longer to get to sleep, perhaps because they weren't yet sleepy enough to fall asleep.

Allik H, Larsson J-O, Smedje H. *Sleep patterns of school-aged children with Asperger syndrome or high functioning autism.* Journal of Autism and Developmental Disorders 2006, 36: 585-595.

Meltzer LJ, Mindell JA. *Sleep and sleep disorders in children and adolescents.* Psychiatric Clinics of North America 2006, 29: 1059-1076.

Melatonin. The Review of Natural Products. Facts & Comparisons. 2002. St. Louis, MO: Kluwer.

Resources for sleep deprived parents

Sleep Better! A Guide to Improving Sleep for Children with Special Needs by V. Mark Durand, Ph.D. Published by Paul H. Brooks Publishing (1998). ISBN 1-55766-315-7

Take Charge of Your Child's Sleep: The All-in-One Resource for Solving Sleep Problems in Kids and Teens by Judith A. Owens & Jodi A. Modell. Published by Marlowe & Co. (2005). ISBN: 156924362X

Good Night, Sweet Dreams, I Love You: Now Get Into Bed and Go to Sleep! by Patrick C. Friman. Published by Boys Town Press (2005). ISBN: 1889322652

Healthy Sleep Habits, Happy Child: A Step-by-Step Program for a Good Night's Sleep by Marc Weissbluth. Published by Ballantine Books (2003). ISBN: 0449004023

Monkey see, monkey do: The link between mirror neurons and joint attention

Who would have thought that a bunch of apes would be responsible for one of the most important scientific discoveries in the last decade. And that the discovery would help explain what goes wrong in the language and social communication skills of people with autism.

It all goes back to the early 1990s when a group of Italian researchers found some previously unknown neurons (brain cells) in the monkeys they were studying. The neurons "fired" in the brains of the monkeys when they observed another monkey (or a person) doing something on purpose, like picking up a piece of food. The scientists soon found that a monkey's neurons also fired if he imitated the movement of another monkey or person. These brain cells were dubbed "mirror neurons."

When they tried the tests in humans, they discovered a very complicated mirror neuron system, one that not only controls movement but that is also associated with social communication and language.

One day, a boy with high functioning autism was recruited to take part in an experiment. The first test used was the electroencephalogram or EEG, a test that creates tracings of the electrical activity in the brain. Mirror neurons cause one type of electrical activity (mu waves) to disappear when the mirror neuron system is activated.

In the boy with autism, the mu wave was still visible when he looked at somebody moving deliberately. It appeared that his mirror neuron system wasn't working. Several other researchers then tried the same test with many children with Autism Spectrum Disorders (ASD) and got the same result.

Today, scientists use functional magnetic resonance imaging or MRI (a test that demonstrates brain cell activity when the patient is given a task to perform) to visualize the neurons as they fire. And they have learned that not only do the mirror neurons fire when witnessing or imitating deliberate movement, but also when a person just imagines making the movement. It may help explain what goes wrong in the language and social communication skills of people with autism.

"Mirror neurons are activated not only when we act (cry or cheer, for example) but also when we observe the actions of others," says Susan Bryson, a leading authority on attention, emotion and learning in autism.

"This 'mirroring' of brain activation allows the observer to 'simulate' and thus share the action and associated emotional states of others. It's the absence of this activation that makes it difficult for individuals with autism to relate directly to the experiences of others."

We don't yet know if the mirror neuron system is absent in people with autism or if it just isn't working. If the latter, it's possible that treatments could be devised to induce function. Understanding how the mirror neuron system works could also speed diagnosis, making it possible to intervene much earlier, even with young infants.

Iacoboni M, Dapretto M. *The Mirror Neuron System and the Consequences of its Dysfunction.* Nature Reviews/Neuroscience 2006, 7: 942-951.

Rizzolatti G, Fogassi L and V Gallese. *Mirrors in the Mind.* Scientific American. November 2006, 54-61.

Ramachandran VS, Oberman LM. *Broken Mirrors.* A Theory of Autism. Scientific American. November 2006, 63-69.

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diagnostic test is effective and cost-efficient. It should happen within the next 10 years for sure.

It will have a big impact on the quality of life for these children. We won't have to rely so heavily on behavioral information, which is the biggest stumbling block now to getting an early diagnosis. And with an early diagnosis, we can intervene earlier to change the life course of the disorder and to reduce the severity of the symptoms so that these children can live more typical lives.

Q. How do you answer the criticism from some people that, far from a "breakthrough" that brings us closer to knowing the cause of autism, these latest findings merely prove how big a mystery autism is? Just how big is the challenge ahead of you?

A. There is some truth to what they say. We're getting closer but we're also getting farther away because it opens up more questions that we didn't have before. But at least they're the right questions and that's a step forward. As far as the challenge that lies ahead, it's a big challenge, but ever so slightly less challenging than it was the day before yesterday.

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CAIRN
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