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Reviewing biomedical and educational research in the field of autism and related disorders

More evidence of GI issues reported in kids with ASD

A new study adds to evidence that gastrointestinal (GI) symptoms are common in children with autism spectrum disorders (ASD) and can contribute to behavior, sleep, and attention problems.

Bibiana Restrepo and colleagues evaluated 255 children with ASD (184 males and 71 females) between 2 and 3.5 years of age, comparing them to 129 age-matched neurotypical controls. Pediatricians gave each child a medical examination, took a medical history, and interviewed caregivers to identify any GI problems the children were experiencing, such as abdominal pain, gas/bloating, diarrhea, constipation, pain when having a bowel movement, vomiting, difficulty swallowing, or the presence of blood in stool or vomit.

Nearly 48% of children with ASD were reported by caregivers to have GI problems, compared to fewer than 18% of controls. Approximately 30% of children with ASD experienced multiple GI symptoms, compared to approximately 5% of controls.

GI symptoms were equally common in boys and girls in both the ASD group and neurotypical controls, and there were no differences in developmental or adaptive measures associated with GI symptoms within either group. However, GI symptoms were associated with behavior, sleep, and attention problems both in children with ASD and in controls (although the behaviors were significantly more severe in the group with ASD). In the ASD group, an increased number of GI symptoms was associated with physical pains, shorter sleep, an increase in self-injurious behaviors, and an increase in parasomnias (abnormal movements, behaviors, or emotions during sleep).

The researchers say, "Our results contribute to a growing body of evidence suggesting that the presence of somatic complaints, behavioral and sleep problems may be triggered or worsened by coexisting medical issues such as GI discomfort." They add, "Compared to the large number of parents of young children with ASD reporting GI symptoms, only a small subset of participants [had] a formal diagnosis suggesting that a

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Cells that line blood vessels implicated in one form of autism

A new study implicates defects in endothelial cells, which are the cells that line blood vessels, as a cause of behavioral symptoms in individuals with a gene disorder linked to autism.

In the study, Baptiste Lacoste and his team (including first author Julie Ouellette) studied mice with a 16p11.2 deletion, which is one of the most common genetic mutations seen in individuals with ASD. In addition, they studied cells derived from the tissue of humans with ASD who have this mutation.

Normally, blood flow rapidly increases to areas of the brain where heightened neural activity is occurring, a process called *neurovascular coupling*. However, in mice with the 16p11.2 deletion, the vascular responses to activated brain regions were slower and weaker.

The researchers found that this problem originated in the blood vessels themselves—and specifically, in the endothelial cells. They also found that the abnormality begins early in life. In petri dish experiments, both human and mouse endothelial cells with the 16p11.2 deletion failed to sprout the extensions that normally allow the vascular network to grow, and the researchers observed the same failure in the endothelial cells of newborn "autistic" mice.

As the mice aged, other cells in the brain compensated for their abnormal endothelial cells, allowing them to develop a full network of blood vessels. However, these vessels remained dysfunctional.

Lacoste comments, "It's a bit like if a plumber comes to your house and does a bad job installing the pipes. You will have trouble getting the right water pressure in your sink from then on."

To demonstrate that endothelial problems caused behavioral abnormalities in the mice with the mutation, the researchers created mice that expressed the mutation in their endothelial cells but not in other cells. These mice exhibited the same deficits in vascular development as "whole-body" mutants, and also displayed hyperactivity, stereotypic movements, and motor learning impairments.

The researchers also found that the effects of the 16p11.2 deletion were more pronounced in male mice, indicating that female mice have mechanisms to help compensate for the defect.

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"Vascular contributions to 16p11.2 deletion autism syndrome modeled in mice," Julie Ouellette, Xavier Toussay, Cesar H. Comin, Luciano da F. Costa, Mirabelle Ho, María Lacalle-Aurioles, Moises Freitas-Andrade, Qing Yan Liu, Sonia Leclerc, Youlian Pan, Ziying Liu, Jean-François Thibodeau, Melissa Yin, Micael Carrier, Cameron J. Morse, Peter Van Dyken, Christopher J. Bergin, Sylvain Baillet, Christopher R. Kennedy, Marie-Ève Tremblay, Yannick D. Benoit, William L. Stanford, Dylan Burger, Duncan J. Stewart, and Baptiste Lacoste, *Nature Neuroscience*, July 13, 2020 (online). Address: Baptiste Lacoste, blacoste@uottawa.ca.

—and—

"Vascular development may be at risk in autism," news release, The Ottawa Hospital, July 13, 2020.

"Genetic wrinkles" in DNA may explain some cases of ASD

Researchers in Canada report that expanded tandem DNA repeats—what they dub "genetic wrinkles" in DNA—may play a significant role in autism spectrum disorders (ASD).

Stephen Scherer and his team, including first author Brett Trost, note that while many genes are known to be associated with autism, these genes explain fewer than 20% of cases. A new technique invented by study coauthor Ryan Yuen allowed the researchers to search for specific characteristics within DNA itself and compare patterns found in individuals with ASD to their parents or other controls.

Tandem repeats are nucleotides (building blocks of DNA) repeated next to each other two or more times. Using their new approach to analyze more than 20,000 genomic samples, the team discovered that tandem repeats in parents sometimes are doubled or even tripled in children with ASD, meaning that a tandem repeat present in a parent's DNA can be expanded in a child. The larger the expansion, the more likely it is that it may alter gene function.

The researchers found that children with ASD were significantly more likely to have

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Wearing compression garments may improve behavior, posture of some individuals with ASD

Full-body compression garments may significantly improve the posture and behavior of some individuals with autism spectrum disorders (ASD), according to a new study.

Vincent Guinchat and colleagues note that compression garments are already used for individuals with joint hypermobility, including those with Ehlers-Danlos syndrome—a syndrome sometimes associated with autism. In this study, the researchers explored whether the garments would also benefit individuals with ASD, severe behavior problems, and severe proprioceptive dysfunction (SPD). Proprioception involves the understanding of where the body is in space, and abnormalities seen in SPD include hypotonia, hypertonia, abnormal posture, poor balance and motor control, and stereotyped behaviors such as spinning.

The researchers analyzed results for 14 children and adults treated with compression garments at their facility. All participants had severe behavior problems that had not responded to multiple forms of treatment, and clinicians had performed extensive testing to rule out possible medical explanations.

The customized compression garments used by the researchers included pants, vests, and mittens, and allowed for a full range of motion. Participants wore them for at least one hour each day, but typically for at least 4 hours and often the entire day, for six weeks. They were not allowed to sleep in them (although several participants wanted to).

The researchers report that individuals wearing the garments exhibited significant improvement in most scores on the Aberrant Behavior Checklist following their use. In particular, scores for irritability, hyperactivity, and lethargy improved. In addition, the participants' posture and motor performance showed significant improvement. However, no changes were seen in sensory scores. While some of the participants also had joint hypermobility, there was no difference in outcome between participants with or without this issue.

The researchers say participants tolerated the garments well. Only one adverse effect—mild edema—was seen in a participant who was allowed to sleep in the garment.

They conclude, "Compression garments appear to be a promising adjuvant treatment for both behavioral and postural impairments in individuals with autism and SPD."

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"Compressive garments in individuals with autism and severe proprioceptive dysfunction: a retrospective exploratory case series," Vincent Guinchat, Elodie Vlamynck, Lautaro Diaz, Coralie Chambon, Justine Pouzenc, Cora Cravero, Carolina Baeza-Velasco, Claude Hamonet, Jean Xavier, and David Cohen, *Children*, July 13, 2020 (free online). Address: David Cohen, Department of Child and Adolescent Psychiatry, Reference Centre for Rare Psychiatric Diseases, AP-HP, Groupe Hospitalier Pitié-Salpêtrière, Sorbonne Université, 75006 Paris, France, david.cohen@aphp.fr.

"Genetic wrinkles" in DNA may explain some cases of ASD

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rare genic tandem repeat expansions than unaffected siblings. Repeat expansions were seen in 23.3% of children with ASD versus 20.7% of unaffected siblings, indicating that they may be responsible for as much as 2.6% of ASD risk. The expansions appeared to be further enlargements of tandem repeats that were already large in the parents. A number of affected genes were involved in nervous system development, the cardiovascular system, and muscle tissue.

Scherer compares these expansions to the working of an accordion. "If they stretch out to a certain extent,' he says, "the music that's played by the DNA or by the instrument has a different tone to it, so the genes are really music here. It's a different… song that's played."

The researchers conclude, "Our findings represent a significant advancement in ASD genetics, as we discovered many genes involved in the tandem repeat expansions that had not been previously identified using conventional genomic analyses."

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"Genome-wide detection of tandem DNA repeats that are expanded in autism," Brett Trost, Worrawat Engchuan, Charlotte M. Nguyen, Bhooma Thiruvahindrapuram, Egor Dolzhenko, Ian Backstrom, Mila Mirceta, Bahareh A. Mojarad, Yue Yin, Alona Dov, Induja Chandrakumar, Tanya Prasolava, Natalie Shum, Omar Hamdan, Giovanna Pellecchia, Jennifer L. Howe, Joseph Whitney, Eric W. Klee, Saurabh Baheti, David G. Amaral, Evdokia Anagnostou, Mayada Elsabbagh, Bridget A. Fernandez, Ny Hoang, M. E. Suzanne Lewis, Xudong Liu, Calvin Sjaarda, Isabel M. Smith, Peter Szatmari, Lonnie Zwaigenbaum, David Glazer, Dean Hartley, A. Keith Stewart, Michael A. Eberle, Nozomu Sato, Christopher E. Pearson, Stephen W. Scherer, and Ryan K. C. Yuen, *Nature*, July 27, 2020 (epub prior to print publication). Address: Ryan K. C. Yuen, Genetics and Genome Biology, The Hospital for Sick Children, Toronto, Ontario, Canada, ryan.yuen@sickkids.ca.

—and—

"Breakthrough in autism spectrum research finds genetic 'wrinkles' in DNA could be a cause," Elizabeth St. Philip, Avis Favaro, and Alexandra Mae Jones, CTVnews, July 27, 2020.

—and—

"Individuals with autism more likely to have expanded tandem DNA repeats," genomeweb.com, July 27, 2020.

Participants needed for ASD microbiome study

Researchers at Massachusetts General Hospital, Harvard Medical School, and the Autism Research Institute are investigating whether the reason why boys are more affected than girls is related to differences in intestinal bacteria.

We are seeking families to participate in this study who have boy and girl siblings with autism. These families will be mailed stool kits with instructions and will be asked to collect samples. A brief medical history will be taken.

For additional information and enrollment details, please contact Harland Winter, MD by phone, 617-724-2004, or by email at GenderDimorphism@autism.com.

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In collaboration with the Schafer Autism Report, the Autism Research Institute publishes an e-newsletter titled *Clinical Research in Autism*. This newsletter provides online links to up-to-date clinical research related to patient care and is designed for pediatricians, nurses, and obstetricians (although other readers are welcome as well). You can subscribe here:

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https://www.autism.org/ari-monthly-e-newsletter/

EDITORIAL: Stephen M. Edelson, Ph.D.

Debating the Role of Genetics in Autism

The history of autism is replete with arguments about its underlying causes and treatments—and frequently over the past 50 years, these arguments have involved genetics.

While it is generally accepted that genes play a major and possibly a primary role in autism, we do not yet know how large this role is. It is an important question for us to answer, because it has direct implications with respect to prevention as well as intervention. In this editorial, I look at how far we have come in understanding genetic influences on autism and what we still need to learn.

The first major genetics debate

Dr. Bernard Rimland was the first person to popularize the view that genetics play an important role in autism spectrum disorders (ASD). In his 1964 seminal book, *Infantile Autism: The Syndrome and Its Implications for a Neural Theory of Behavior*, he single-handedly debunked the then-popular theory blaming emotional neglect by parents and argued convincingly that autism has an underlying biological basis. Besides genetics, he postulated that neurology and environmental factors are likely contributors to autism.

About a dozen years later, Folstein and Rutter (1977) published the first convincing data to support a genetic component of autism. Basically, they reported a high prevalence rate of autism in 11 monozygotic twins, (who have essentially a 100% genetic overlap) as compared to a much lower rate in 10 dizygotic twins (who have essentially a 50% genetic overlap).

The current debates

Today, approximately 20% of individuals with ASD have a known genetic autism-related syndrome. These individuals are often referred to as having "syndromic autism." Autism-linked syndromes include Angelman, Fragile X, Landau-Kleffner, and Rett's syndromes as well as less conmon syndromes caused by other mutations.

We do not yet know what role genes play for the remaining 80% of individuals with ASD. They may have yet-to-be-identified genetic syndromes; they may have ASD due to a genetic-environmental interaction; or they may have ASD caused by something entirely unrelated to their genetic makeup.

The debate about the exact role of genetics in autism is currently receiving much media attention. More than 100 genes have been reported to be associated with autism during the past two decades, but there is still no primary "autism gene" or set of "autism genes" that determines with high likelihood whether an individual will be on the autism spectrum.

There is also considerable debate over the role of environmental toxins and how they may interact with gene expression. One theory is that a relatively small number of people are genetically susceptible to relatively low levels of toxic substances that are now common in the environment. Notably, many research studies have reported increased risks of autism near highways with high levels of particulate matter (which includes ammonia, black carbon, mineral dust, nitrates, sodium chloride, and sulfate), as well as near fields sprayed with pesticides. These toxins could cause damage to the neurological, autonomic, metabolic, or immune system (or multiple systems) in genetically vulnerable individuals, increasing the risk for ASD.

A related theory is that some individuals with ASD have a genetic predisposition to certain nutritional deficiencies that make them more prone to developing autism. For example, there is evidence that a number of children with ASD have difficulty metabolizing folate and can benefit significantly from taking supplements in the form of folinic acid.

If a genetic-environmental connection exists, it could help explain the dramatic increase in the prevalence of autism over the past 50 years. In the early 1970s, autism was diagnosed in about one in two thousand children. Today, the number is about one in fifty-four. While diagnosis has improved significantly, this alone cannot account for such a steep rise in cases.

Given the importance of understanding genetics and the environment, one would think that there would be countless studies investigating *both of them simultaneously in the same individuals*. Unfortunately, few studies in each subfield have employed this scientific approach, and the results of these studies are mixed. This is most likely due to the researchers investigating a rather wide spectrum of individuals with ASD, an approach that is not likely to lead to consistent data. Furthermore, many of these researchers base their conclusions on correlational analyses; but scientifically speaking, such analyses cannot prove a cause-and-effect relationship.

The best way to resolve this important issue is to conduct relatively complex experimental studies by employing valid measurement tools to properly evaluate genetic and environmental factors in the same individuals. It is also critical that correlational studies be followed up with scientifically controlled experiments.

What we can do while we search for answers

Clearly, it will take time for us to elucidate the role that genetics play in causing or exacerbating autism. Even then, the answers will not be simple, because different genes and different environmental factors will be at play in different people. Fortunately, however, there are steps we can take right now to aid individuals with autism—especially if their symptoms may stem in whole or in part from genetic vulnerability. In particular, there are four areas in which we can focus our efforts:

Nutrition. It is becoming clear that many individuals with autism have nutritional deficiencies, and that some of these may be caused or worsened by genetic vulnerabilities (for instance, defects in metabolizing folate or vitamin B12). In-depth testing of individuals with autism can help to uncover any existing nutritional deficiencies and allow us to address them effectively—whether the causes are genetic or not.

Toxins. Reducing the body burden of toxins in individuals with autism will benefit all of them, but especially those with genetic vulnerabilities that make them more prone to damage from these toxins. In addition to addressing major sources of pollution at the government and industry level, we can take personal action by minimizing the use of toxic chemicals in our own homes.

Microbiome optimization. It is becoming clear that many people—not just those with autism—have genetic vulnerabilities that can affect their gut microbiomes in ways that predispose to disease (see Hall et al., *Nature*, 2017). While we may not yet understand the role that genes play in this area, groundbreaking research suggests that dietary changes, fecal transplants, and other interventions can help to normalize gut microbes in individuals with autism and gut dysbiosis.

Early intervention. While genetic anomalies may underlie the behaviors and learning problems of many individuals with autism, we now know that early intervention can dramatically benefit children with ASD no matter what the cause.

In short, we have a long way to go before we fully understand how genes influence autism. But we have powerful tools we can use right now to help many individuals on the spectrum thrive and excel—no matter where the roots of their autism lie.

Research Updates

Widespread vitamin D deficiency again found in childen, teens with ASD

A new study from Turkey adds to evidence that vitamin D deficiency is significantly higher in children and adolescents with autism spectrum disorders (ASD) than in the general population.

Esma Şengenç and colleagues measured serum 25-hydroxyvitamin D (25-OHD) levels in 1,529 children and teens with ASD. In addition, they analyzed calcium, phosphorus, alkaline phosphatase, and 25-OHD levels of 100 of these individuals, comparing them to a neurotypical control group.

The researchers say they detected vitamin D deficiency or insufficiency in approximately 95% of the individuals with ASD. Of these, 58% had vitamin D deficiency and 13% had severe deficiency. Levels of vitamin D were significantly lower in adolescents with ASD than in children younger than 11 years of age.

The researchers say, "Additionally, the mean serum 25-OHD level, which is a measurable indicator of vitamin D, was significantly lower in children and adolescents with autism than in healthy controls." Individuals with ASD also had significantly higher levels of alkaline phosphatase, a marker for vitamin D deficiency.

The researchers note that several earlier studies (although not all) have shown lower vitamin D levels in children with ASD compared to neurotypical peers. They conclude, "Monitoring vitamin D levels is crucial in autistic children, especially adolescents, to take protective measures and treat this condition early."

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"Vitamin D levels in children and adolescents with autism," Esma Şengenç Ertuğrul Kıykım, and Sema Saltik, *Journal of International Medical Research*, Vol. 48, No. 7, July 15, 2020 (free online). Address: Esma Şengenç, Department of Pediatrics, Cerrahpasa Medical Faculty, Istanbul University-Cerrahpasa, No. 53 Koca Mustafapasa St, Istanbul, 34096, Turkey. dresmasengenc@gmail.com.

Does gastrointestinal mucus play a role in ASD?

A recent research review suggests that autism spectrum disorders (ASD) and other neurological conditions may cause changes in gut mucus, and these changes in turn may worsen symptoms of these conditions.

The study's senior author, Elisa Hill-Yardin, notes, "Mucus is a critical protective layer that helps balance good and bad bacteria in your gut, but you need just the right amount—not too little and not too much. Researchers have previously shown that changes to intestinal mucus affect the balance of bacteria in the gut but until now, no one has made the connection between gut mucus and the brain."

The researchers analyzed data from 113 neurological, gut, and microbiology studies. They found that people with ASD, Parkinson's disease, Alzheimer's disease, and multiple sclerosis have different types of bacteria in their gut mucus compared to neurotypical controls, and have different ratios of beneficial and harmful bacteria.

The researchers note that the gut has its own neuronal network, the enteric nervous system, which regulates mucus secretion and renewal. They say, "We propose that factors that influence the nervous system may also affect the volume, viscosity, and porosity of mucus composition and subsequently, gastrointestinal microbial populations." They add, "Since some microbes use mucus as a prominent energy source, changes in mucus properties could alter, and even exacerbate, dysbiosis-related gut symptoms in neurological disorders."

Hill-Yardin concludes, "If we can understand the role that gut mucus plays in brain disease, we can try to develop treatments that harness this precise part of the gut-brain axis."

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"The role of the gastrointestinal mucus in intestinal homeostasis: implications for neurological disorders," Madushani Herath, Suzanne Hosie, Joel C. Bornstein, Ashley E. Franks, and Elisa L. Hill Yardin, *Frontiers in Cellular and Infection Microbiology*, May 28, 2020 (free online). Address: Elisa Hill-Yardin, elisa.hill@rmit.edu.au.

—and—

"New gut-brain link: how gut mucus could help treat brain disorders," Science Daily, May 29, 2020.

Researchers detect autism subtype involving lipids

By combining multiple sources of data, researchers in the U.S. and Israel have identified a form of autism characterized by abnormal levels of fat molecules in the blood.

Isaac Kohane and colleagues, including first author Yuan Luo, began by obtaining data on the expression patterns of exons (areas of genes that encode for proteins) that function together during prenatal brain development. In particular, they focused on exon clusters that are expressed differently between males and females, because autism is more common in males. They then used a separate database to identify autism-related mutations in the exons of individuals with ASD. The researchers found 33 exon clusters that overlapped between the sets of data and discovered that some of the clusters contained exons involved in regulating fatty molecules called lipids.

The researchers next analyzed nearly 3 million medical records from patients at Boston Children's Hospital and found that as a group, children with ASD exhibited unusual blood lipid profiles compared to controls. Finally, the researchers analyzed healthcare claims for more than 34 million people, and found that 6.6% of people with ASD have dyslipidemia (abnormal lipid levels). They also found that parents with a history of dyslipidemia have up to 16% higher odds of having children with ASD.

Luo comments, "Previously, autism subtypes have been defined based on symptoms only—autistic disorder, Asperger syndrome, etc.—and they can be hard to differentiate as it is really a spectrum of symptoms. The autism subtype characterized by abnormal levels identified in this study is the first multidimensional evidenced-based subtype that has distinct molecular features and an underlying cause."

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"A multidimensional precision medicine approach identifies an autism subtype characterized by dyslipidemia," Yuan Luo, Alal Eran, Nathan Palmer, Paul Avillach, Ami Levy-Moonshine, Peter Szolovits, and Isaac S. Kohane, Nature Medicine, August 10, 2020 (epub prior to print publication). Address: Isaac Kohane, Department of Biomedical Informatics, 10 Shattuck Street Suite 514, Boston, MA 02115.

—and—

"Blood lipid levels may be altered in some autistic people," Jonathan Moens, Spectrum News, August 10, 2020.

—and—

"AI-enhanced precision medicine identifies novel autism subtype," news release, Northwestern University, August 10, 2020.

—and—

"New subtype of autism related to fat levels identified by Israeli-US team," Rossella Tercatin, *Jerusalem Post*, August 13, 2020.

ARRI Survey: Seniors with Autism Spectrum Disorder

https://www.autism.com/adult_survey

We hope the results from this survey will provide insight about the needs and challenges faced by seniors with autism (ages 50 and older) and their support providers, and better inform the autism community, government agencies, and other welfare and health-related organizations about this population's quality of life issues.

Research Updates

Social emails of individuals with ASD are atypical

In a letter to the journal *Molecular Autism*, researchers say that emails sent by people with autism spectrum disorders (ASD) indicate that electronic social communication in these individuals is atypical in ways similar to face-to-face social communication.

The authors note, "When scheduling research assessments, we consistently notice an atypical social-communicative style in e-mails from adults with [ASD] compared to non-autistic participants."

"Importantly," they note, "our e-mails sent to autistic and non-autistic adults (e.g., inviting them to participate in a study) are identical; therefore, the groups are broadly age-, gender-, and IQ-matched for the lab-based studies in which they were invited to participate. In addition, our e-mails were neither designed nor structured to elicit a response for formal analysis. Together, this has created a controlled, yet naturalistic, situation for us to compare electronic social communication in adults with and without [ASD]."

The researchers say emails from individuals with ASD typically differ from emails from neurotypical individuals in these ways:

- They have "a noticeable lack of social niceties and preamble," yet are equally polite.
- They pay considerable attention to detail, including correcting grammatical errors made by the researchers.
- They communicate precise but unconventional information about times and locations (for instance, saying they will arrive at 14:08 or using map coordinates to describe locations).

The researchers add that their university students with ASD say they experience significant difficulties in writing socially-related emails, and often misinterpret messages, or are themselves misinterpreted. They also are more likely to fail to respond to emails due to the difficulty in filtering out unimportant information.

The researchers say that based on their observations, "we tentatively propose that atypical electronic social-communicative behavior in autism is in line with many of the social-communicative features of [ASD] observed during social interactions in everyday life." They suggest that research into the electronic communications of individuals with ASD could provide new ways to help identify ASD (for instance, by measuring atypical electronic as well as in-person social communication) and could lead to strategies to help people with ASD and their neurotypical peers communicate more effectively.

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"Electronic communication in autism spectrum conditions," Lucy Anne Livingston, Chris Ashwin, and Punit Shah, *Molecular Autism*, 2020 (free online). Address: Lucy Anne Livingston, School of Psychology, Cardiff University, Cardiff, UK, livingston@cardiff.ac.uk.

Eye saccades smaller in ASD in response to non-social situations

A new study reports that people with autism spectrum disorders (ASD) exhibit abnormalities in gaze-shifting when viewing non-social as well as social stimuli—a finding that indicates that the gaze anomalies are not simply due to low social motivation.

Previous studies revealed abnormalities in rapid eye movements, called saccades, when people with ASD viewed social situations. In the new study, Nico Bast and colleagues tracked saccades in 142 participants with ASD and 142 matched neurotypical controls as they viewed naturalistic scenes with or without people in them. The researchers found that the individuals with ASD had smaller and briefer saccades jumps than controls, whether they viewed natural scenes or people.

Bast says, "Maybe people with autism just have basic perception difficulties to perceive stimuli—any stimuli—that are far away from the direct focus of attention."

Bast and his colleagues say a brain region called the pontocerebellar network, which controls eye movements, may play a role in the altered saccades in autism. They conclude, "We propose altered pontocerebellar motor modulation as [an] underlying mechanism that contributes to atypical oculo-motor coordination and attention function in ASD."

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"Saccade dysmetria indicates attenuated visual exploration in autism spectrum disorder," Nico Bast, Luke Mason, Christine M. Freitag, Tim Smith, Ana Maria Portugal, Luise Poustka, Tobias Banaschewski, and Mark Johnson, *Journal of Child Psychology and Psychiatry*, May 25, 2020 (epub prior to print publication). Address: Nico Bast, Department of Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy, University Hospital, Goethe University Frankfurt am Main, Deutschordenstraße 50, 60528 Frankfurt, Germany, nico.bast@kgu.de.

—and—

"Eye 'jumps' in autistic people may be especially fleeting," Jonathan Moens, Spectrum News, July 9, 2020.

Maternal cannabis use during pregnancy may increase odds of autism

Children of mothers who use cannabis during pregnancy may have increased odds of developing autism spectrum disorders (ASD), according to a new study from Canada.

Using data from a birth registry and health administrative databases, Daniel Corsi and colleagues reviewed information on births in Ontario between April 1, 2007 and March 31, 2012, before recreational cannabis was legalized. Of the half million women for whom data was available, 0.6% reported using cannabis while pregnant.

The researchers found that the incidence of autism in these women's children was 4.00 per 1,000 person-years, compared to 2.42 for unexposed children. When they looked specifically at data for women who used cannabis and no other substances such as cigarettes, alcohol, or tobacco, the risk remained elevated. In addition, the researchers say, "The incidence of intellectual disability and learning disorders was higher among offspring of mothers who used cannabis in pregnancy, although less statistically robust."

In earlier research, Corsi and colleagues found that cannabis use during pregnancy was linked to an increased risk of preterm birth.

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"Maternal cannabis use in pregnancy and child neurodevelopmental outcomes," Daniel J. Corsi, Jessy Donelle, Ewa Sucha, Steven Hawken, Helen Hsu, Darine El-Chaâr, Lise Bisnaire, Deshayne Fell, Shi Wu Wen, and Mark Walker, N*ature Medicine*, August 10, 2020 (online). Address: Daniel Corsi, dcorsi@ohri.ca.

—and—

"Cannabis use in pregnancy linked to a greater risk of autism," news release, The Ottawa Hospital, August 10, 2020.

Need help or information?
The Autism Research Institute maintains a toll-free calling center:

833-281-7165

Are you new to autism?

If so, the Autism Research Institute has valuable information on seeking appropriate medical care. For a list of important questions to ask a potential medical provider, see:

https://www.autism.org/finding-a-clinician/

Study reports tau anomalies in genetic condition causing autism, hints at possible treatment

Early in 2020, researchers reported that lowering levels of a protein called *tau* reduced symptoms in two mouse models of autism and epilepsy (see ARRI 2020, No. 2). Now, a new study by a separate group of scientists indicates that normalizing the effects of tau may ameliorate symptoms of another form of autism.

Illana Gozes and colleagues, including first author Iris Grigg, found deposits of tau—a protein associated with Alzheimer's disease—in postmortem tissue from the brain of a seven-year-old child with autism. The child had ADNP syndrome, a genetic disorder that causes autistic symptoms and other mental and physical symptoms and is responsible for about 0.2% of cases of autism overall.

The researchers tested an experimental Alzheimer's drug called NAP on nerve cells carrying an ADNP mutation similar to that seen in the child's tissues. Gozes says, "NAP is actually a short active fragment of the normal ADNP protein. When we added NAP to the nerve cells carrying an ADNP mutation, the tau protein bound to the nerve cell skeleton properly, and the cells returned to normal function."

She adds, "The fact that NAP treatment has been successful in restoring the normal function of neuronal-like cell models with impaired ADNP raises hopes that it may be used as a remedy for ADNP syndrome and its severe implications, including autism. Moreover, because other genetic disorders related to autism are characterized by tau pathologies in the brain, we hope that those suffering from these syndromes will also be able to benefit from NAP treatment in the future."

To further understand the effects of the mutation that causes ADNP syndrome, the researchers extracted messenger RNA from the tissues of the deceased child and analyzed about 40 proteins in the child's tissue encoded by the mRNA. In addition, they analyzed protein expression in white blood cells taken from three other children with the syndrome. The researchers found a variety of characteristics that were common to the children with the syndrome but very different from the normal appearance of these proteins.

Gozes says, "[The] significance of these findings is that the mutation that causes ADNP syndrome damages a wide range of essential proteins, some of which bind to the tau protein, among other things, and impair its function as well. This creates various pathological effects in the brains and other tissues of children with ADNP syndrome, one of which is the formation of tau deposits, known to be a characteristic of Alzheimer's disease."

She adds that the findings offer hope that "we will ultimately reach the goal of developing a drug or drugs that will help children with autism resulting from genetic mutations."

In the earlier research by Chao Tai and colleagues, the researchers found that reducing levels of tau prevented seizures and symptoms of autism in a mouse model of Dravet syndrome—a severe form of epilepsy—as well as reducing symptoms in a second mouse model of autism involving a different genetic mutation.

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"Tauopathy in the young autistic brain: novel biomarker and therapeutic target," Iris Grigg, Yanina Ivashko-Pachima, Tom Aharon Hait, Vlasta Korenková, Olga Touloumi, Roza Lagoudaki, Anke Van Dijck, Zlatko Marusic, Mirna Anicic, Jurica Vukovic, R. Frank Kooy, Nikolaos Grigoriadis, and Illana Gozes, *Translational Psychiatry*, July 2020 (free online). Address: Illana Gozes, Elton Laboratory for Neuroendocrinology, Department of Human Molecular Genetics and Biochemistry, Sackler Faculty of Medicine, Sagol School of Neuroscience and Adams Super Center for Brain Studies, Tel Aviv University, Tel Aviv, Israel, igozes@tauex.tau.ac.il.

—and—

"Experimental drug for Alzheimer's may help children with autism," news release, Tel Aviv University, July 28, 2020.

—see also—

"Tau reduction prevents key features of autism in mouse models," C. Tai, C. W. Chang, G. Q. Yu, I. Lopez, X. Yu, X. Wang, W. Guo, and L. Mucke, *Neuron*, February 18, 2020 (epub prior to print publication). Address: lennart.mucke@gladstone.ucsf.edu.

The Kids First Initiative

The Hartwell Foundation Kids First initiative seeks to help every family who has a child with an autism spectrum disorder. The goal is to create detailed categories that accurately reflect individual behavior and personality, with the expectation of advancing personalized, targeted approaches for care and intervention that will be more successful than what is available today.

The Kids First approach is conducted using IRB-approved confidential survey methodology by prominent universities. Survey questions are simple, focused on basic behavioral and medical information, and can be completed in about 10 minutes. Results will be shared confidentially with all survey participants. The collected data will provide a unique opportunity for researchers to begin classification of ASD, and as new categories are identified, the effort will expand to more sophisticated requests for information.

We invite you to participate in the Kids First confidential survey, joining a growing network of families, clinicians, and scientists involved in this innovative research project to improve the lives of children and families affected by ASD. To learn more and begin your survey, visit kidsfirst.stanford.edu and when asked, type ARI as your referral code.

Coping with COVID-19

To aid individuals with autism and their families during the COVID-19 pandemic, ARI is offering these resources:

- Free presentations offering evidence-based strategies to manage at home during extended school closures.
- Social stories and short videos on hygiene and medical procedures.
- Physician resources for supporting patients diagnosed with autism.

To view these, as well as to see first-person stories by families about how they are dealing with this crisis, visit this link:

https://www.autism.org/covid-19-resources/

Quotable....

"Physical health comorbidities occur significantly more frequently in individuals with ASD than in the wider general population. Such comorbidities include neuroinflammation and immune dysregulation, GI dysfunction, metabolic abnormalities, acquired mitochondrial dysfunction and oxidative stress as well as seizure disorders such as epilepsy. Some of the physical symptoms presented by those with ASD have been erroneously attributed to the core behavioural and neurological features of ASD.... It is of utmost importance to raise awareness among healthcare professionals and bridge the gap between physical health and the implication of ASD as a whole body disorder. Leaving these physical conditions undiagnosed and untreated clearly results in health inequalities. They can also significantly decrease a person's quality of life potentially leading to morbidity and/or premature mortality."

"Bridging the gap between physical health and autism spectrum disorder," R. Sala, L. Amet, N. Blagojevic-Stokic, P. Shattock, and P. Whiteley, *Neuropsychiatric Disease and Treatment*, June 30, 2020

Internships, work experience can increase independence

Business-based internships and competitive employment in the community can significantly improve the independence of young adults with autism spectrum disorders (ASD), according to a new study.

Carol Schall and colleagues enrolled 156 individuals with ASD in this study, dividing them roughly evenly into control and treatment groups. Control group participants remained in their high schools for the school year prior to graduation and received the services outlined in their individualized education programs (IEPs). Participants in the treatment arm did not attend high school but instead participated in a program called Project SEARCH plus ASD Supports (PS+ASD). This group received 35 hours a week of employment training in a community business. In addition, they rotated through three 10- to 12-week unpaid internships in the business. "During this year," the researchers say, "[participants] spent approximately 900 hours of time in a community business with approximately 720 hours of time in internship activities."

The researchers say that at the beginning of the study, participants in both groups needed relatively high levels of behavioral support and required significant prompting to do tasks. "Further," they say, "few individuals in either group were able to engage in everyday problem solving, ask for help when needed, demonstrate personal safety skills, use public transportation, or demonstrate work-appropriate social behaviors." All were in self-contained special education programs at the start of the study.

In an earlier study involving the same participants, the researchers reported that employment outcomes for the treatment group were significantly better than for controls, with 73.4% acquiring and maintaining employment within one year after graduation compared to 17% of controls. In this study, they report that individuals in the treatment group also demonstrated improvement in all domains of the Supports Intensity Scale-Adult Version (SIS-A), which evaluates the intensity of support needed by an individual with a disability. In contrast, individuals in the control group improved in only one domain on the SIS-A. Moreover, individuals in the treatment group continued to improve during the year following graduation from the program, while the control group plateaued. Notably, individuals in the treatment group also improved their traditional academic skills at a greater rate than those who remained in school.

The researchers comment, "These results indicate that individuals with ASD gain independence as a result of competitive employment, rather than increased independence being related to the acquisition of employment." They conclude, "The findings in this study should provide support for the continued policy emphasis on competitive integrated employment as the first choice of employment for transition-aged youth with ASD."

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"The effect of business internships model and employment on enhancing the independence of young adults with significant impact from autism," Carol Schall, Adam P. Sima, Lauren Avellone, Paul Wehman, Jennifer McDonough, and Alecia Brown, *Intellectual and Developmental Disabilities*, Vol. 58, No. 4, 2020 (free online). Address: Carol Schall, Virginia Commonwealth University, Autism Center for Excellence, Box 842011, Richmond, VA 23284-2011, cmschall@vcu.edu.

Free Autism Continuing Education and Webinars

Free Certificates of Participation are available upon passing an online quiz for most webinars. Some events offer Continuing Education Units and/or Continuing Medical Education credits.

—October 1, 2020—
1 p.m. Eastern Time
The Sensory Smart Child
Lindsey Biel, M.A., OTR/L

—October 21, 2020—
1 p.m. Eastern Time
How the Autonomic Nervous System May Govern Anxiety in Autism
Emily Casanova, Ph.D., and Manuel Casanova, M.D.

—February 10, 2021—
1 p.m. Eastern Time
The Role of Neurotransmitters in GI Disorders Related to Autism
Kara Gross-Margolis, M.D.

Space is limited—watch your email, or visit us on Facebook and Twitter for updates and registration links. You can view previous webinars at https://www.autism.com/webinars.

** We are grateful to our friends at the Johnson Center for Child Health & Development for working in partnership to offer presentations.*

More evidence of GI issues reported in kids with ASD

(cont. from page 1)

large proportion of young children with GI symptoms are not being recognized and treated."

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"Developmental-behavioral profiles in children with autism spectrum disorder and co-occurring gastrointestinal symptoms," Bibiana Restrepo, Kathleen Angkustsiri, Sandra L. Taylor, Sally J. Rogers, Jacqueline Cabral, Brianna Heath. Alexa Hechtman, Marjorie Solomon, Paul Ashwood, David G. Amaral, and Christine Wu Nordahl, *Autism Research*, August 6, 2020 (free online). Address: Bibiana Restrepo, Division of Developmental and Behavioral Pediatrics, Department of Pediatrics, University of California at Davis School of Medicine, Sacramento, CA 95817, bmrestrepo@ucdavis.edu.

—In Memoriam—

Edward Ritvo, M.D. passed away on June 10, 2020 at the age of 90. He was a pioneering researcher in the field of psychiatry, specializing in autism.

Through years of research, Dr. Ritvo was the first to scientifically prove that autism was a neurological disease with a genetic component, and not a psychological disease as had been previously thought. He spent most of his career as a senior administrator, teacher, and mentor at UCLA's prestigious Neuropsychiatric Institute.

Dr. Ritvo lectured and taught extensively on autism and child development throughout the world and was a consultant to the FDA and numerous school districts, corporations, and governmental entities. His work continued throughout his entire life, including pioneering work through telemedicine (telepsychiatry), and a recently published article that describes a possible diagnostic biomarker for autism, which was the culmination of studies he began early in his career.

Dr. Ritvo was one of the true giants in the autism field, and he will be missed.

Cell Danger Response Biology—New Perspective

A new paper, partially funded by ARI, describes cell danger response biology—the new science that connects environmental health with mitochondria and the rising tide of chronic illness. You can read the paper at:

https://www.autism.org/cell-danger-response/

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—About ARI—

The Autism Research Institute (ARI) is the oldest autism research organization in the world, founded by Dr. Bernard Rimland in 1967.

ARI'S WORK INCLUDES:

Conducting and sponsoring research on the causes of and best treatments for autism (more than $200,000 in research grants awarded last year), with a focus on research that can translate rapidly into help for today's autistic children and adults and their families.

•

Networking researchers, physicians, and parents to speed the development and dissemination of safe and effective treatment methods.

•

Hosting webinars and one of the largest informational websites on autism in the world.

•

Sponsoring one or two major think tanks a year, involving researchers and experienced clinicians.

ARI's work relies on charitable contributions from individuals and organizations. All donations are tax deductible. We are proud to have earned Charity Navigator's highly respected "Four Star Award" for fiscal management, accountability, and transparency.

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