

Autism Research Review

I N T E R N A T I O N A L

A quarterly publication of the Autism Research Institute—www.Autism.org

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

Diffusion MRI study reveals differences between brains of individuals with ASD and controls

Researchers in the United States report that by using a technique called diffusion MRI—which measures the movement of water molecules in tissues, helping researchers to see their microarchitecture—they are able to identify structural differences between the brains of individuals with autism spectrum disorders (ASD) and neurotypical controls.

Utilizing this technique, Benjamin Newman and colleagues analyzed scans of 148 adolescents and adults diagnosed with ASD and 124 neurotypical controls. All of the participants were enrolled in the Autism Centers for Excellence Network.

“What we’re seeing,” Newman says, “is that there’s a difference in the diameter

of the microstructural components in the brains of autistic people that can cause them to conduct electricity slower. It’s the structure that constrains how the function of the brain works.” The researchers also found evidence that the microstructural differences they detected are directly related to participants’ scores on the Social Communication Questionnaire, a clinical tool for diagnosing autism.

Newman and colleagues say their findings suggest that alterations in the structure of axons in the brain, and a resulting slowdown in conduction velocity, “are widespread throughout the brain and may contribute to the clinical picture of ASD.” In addition, they say their results may help to shed light on recent findings suggesting that ASD involves deficits in long-range con-

nections in the brain and an overreliance on shorter-range or local connections. “If the underconnectivity theory of ASD is accurate,” they say, “it is likely that observed functional connectivity changes have a basis in the cellular microstructure of the neurons.”

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“Conduction velocity, G-ratio, and extracellular water as microstructural characteristics of autism spectrum disorder,” Benjamin T. Newman, Zachary Jacokes, Siva Venkadesh, Sara J. Webb, Natalia M. Kleinhans, James C. McPartland, T. Jason Druzgal, Kevin A. Pelphrey, and John Darrell Van Horn, *PLOS One*, April 17, 2024 (free online). Address: John Darrell Van Horn, jdV7g@virginia.edu.

—and—
“Study identifies new metric for diagnosing autism,” Russ Bahorsky, news release, University of Virginia, April 17, 2024.

Individuals with ASD may be more vulnerable to PTSD

Individuals with autism spectrum disorders (ASD) may be especially vulnerable to developing post traumatic stress syndrome (PTSD), according to a new study by researchers in Australia and France.

Alice Shaam Al Abed and colleagues found that in four different mouse models of ASD, exposure to a mildly stressful event induced PTSD-like memory. Control mice, on the other hand, developed PTSD only under extreme stress. The researchers also found that PTSD caused social deficits and repetitive behaviors to become more pronounced in the autism-model mice.

The researchers discovered that the formation of PTSD-type memories in the autism-model mice stemmed from an overactivation of the prefrontal cortex, which was associated with alterations in the activity of neurons called parvalbumin interneurons. Study coauthor Nathalie Dehorter says, “We identified specific cortical circuit alterations that trigger the switch between the formation of a normal memory and a PTSD-like memory during stress.”

The researchers also report that they could successfully treat the autism-model mice that developed PTSD by using behav-

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Large study detects no link between use of acetaminophen in pregnancy and ASD, ADHD, intellectual disability diagnoses

While previous research has suggested an association between maternal use of acetaminophen during pregnancy and autism spectrum disorders (ASD), a new large-scale study from Sweden and the United States did not identify a link between the two.

Viktor Ahlqvist and colleagues analyzed data from a nationwide cohort of more than 2.4 million children born in Sweden, fol-

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When the researchers studied sibling pairs in which one sibling was exposed prenatally to acetaminophen and the other was not, they found no increased likelihood of ASD, ADHD, or intellectual disability in exposed children.
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lowing each child up to 26 years after birth. Initially, they detected a small increase in the likelihood of children being diagnosed with ASD, attention-deficit/hyperactivity (ADHD), or intellectual disability if their mothers had taken acetaminophen during pregnancy. However, when the researchers studied sibling pairs in which one sibling

was exposed prenatally to acetaminophen and the other was not, they found no increased likelihood of the conditions in exposed children.

The researchers say that studying sibling pairs, who share a substantial portion of their genes as well as environmental factors, makes it easier to control for genetic and environmental variables. The difference between their findings and earlier research, the researchers say, “suggests that associations observed in other models may have been attributable to familial confounding.”

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“Acetaminophen use during pregnancy and children’s risk of autism, ADHD, and intellectual disability,” Viktor Ahlqvist, Hugo Sjöqvist, Christina Dalman, Håkan Karlsson, Olof Stephansson, Stefan Johansson, Cecilia Magnusson, Renee M. Gardner, and Brian K. Lee, *Journal of the American Medical Association*, April 9, 2024 (online). Address: Viktor H. Ahlqvist, Department of Global Public Health, Karolinska Institutet, Stockholm, Sweden. viktor.ahlqvist@ki.se.

—and—
“No link between acetaminophen use during pregnancy and cognitive risks, says large sibling study,” news release, Drexel University, April 9, 2024.

Mouse study offers new clues about interrelationship of ASD, GI problems, and social behavior

A study conducted by researchers at the Utah School of Medicine offers insights into the association between autism spectrum disorders (ASD) and gastrointestinal (GI) problems, which affect up to 85% of people with ASD. The study also indicates that GI problems may play a causal role in social impairments in ASD, and suggests that two specific types of gut microbes might help to ease GI symptoms.

In the study, D. Garrett Brown and colleagues first dosed mice repeatedly with a substance that produced bouts of colitis, and then examined the behavior of the mice after they recovered. The researchers found that animals that experienced repeated colitis did not appear sick, anxious, or depressed afterward, did not exhibit compulsive behaviors, and did not exhibit significant changes in activity. However, the mice did have much less desire to engage in social interactions with new mice. “Overall,” the researchers say, “these data suggest that past, repeated GI insults are associated with abnormal social interactions in mice.”

Next, the researchers explored whether the gut microbiota of individuals with ASD might harbor microbes that make them more vulnerable to GI disease and, as a result, to

impairments in social behavior. To investigate this issue, the researchers transplanted fecal samples from five individuals with ASD into mice, using fecal samples from neurotypical family members as controls. They then induced colitis in the offspring of the mice. They report, “Analysis of the data when grouped by family revealed that the microbiota from all but one individual with ASD consistently worsens either weight loss, colon shortening [a sign of damage], or both when compared to the respective familial controls.” They conclude that “in most cases, microbiotas from individuals with ASD worsen GI symptoms.”

The researchers also identified two bacterial organisms—*Bacteroides uniformis* and species of *Blautia*—that appeared to be protective. “Oral treatment with either of these microbes,” they say, “reduces colon injury in mice.” In addition, they say, treatment with a *Blautia* isolate from a neurotypical control ameliorated gut injury-associated social engagement deficits in the mice.

Brown and his team say, “Collectively, our data demonstrate that past intestinal distress is associated with changes in active social behavior in mice that can be amelio-

rated by supplementation of members of the human microbiota.”

The researchers note that while fecal microbiota transplants (FMTs) are currently being tested as a treatment for several conditions including ASD (see page 3), “the complexity of an FMT makes it difficult to obtain reproducible donor microbiotas.” Moreover, they say, there is also the possibility of transferring dangerous microbes into the recipient. “Thus,” they say, “the identification of specific microbiota members that can ameliorate GI symptoms and modify neurological manifestations will be important for future management of these disorders.”

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“Colitis reduces active social engagement in mice and is ameliorated by supplementation with human microbiota members,” D. Garrett Brown, Michaela Murphy, Roberto Cadeddu, Rickesha Bell, Allison Weis, Tyson Chiaro, Kendra Klag, Jubel Morgan, Hilary Coon, W. Zac Stephens, Marco Bortolato, and June L. Round, *Nature Communications*, March 30, 2024 (free online). Address: June Round, Department of Pathology, University of Utah School of Medicine, Huntsman Cancer Institute, Division of Microbiology and Immunology, Salt Lake City, UT, june.round@path.utah.edu.

Individuals with ASD may be more vulnerable to PTSD (continued from page 1)

ioral therapy. Normalizing PTSD-like memory, they say, also led to a reduction in social deficits and repetitive movements.

Their study, the researchers say, provides evidence that individuals with ASD may develop PTSD under levels of stress that are not considered extreme. In addition, they say, it emphasizes the importance of identifying PTSD early in individuals with ASD, because PTSD is strongly associated with comorbid psychological issues and suicide.

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“Parvalbumin interneuron activity in autism underlies susceptibility to PTSD-like memory formation,” Alice Shaam Al Abed, Tiarne Vickie Allen, Noorya Yasmin Ahmed, Azza Sellami, Yovina Sontani, Elise Caitlin Rawlinson, Aline Marighetto, Aline Desmedt, and Nathalie Dehorter, *iScience*, May 17, 2024 (free online). Address: Alice Shaam Al Abed, IECCL Institute of Neuroscience, John Curtin School of Medical Research, The Australian National University, Canberra, ACT, Australia, shaam.alabed@anu.edu.au.

—and—
“Study shows heightened sensitivity to PTSD in autism,” news release, Queensland Brain Institute, May 3, 2024.

Did you know? The Autism Research Institute recently received its fifth annual four-star rating—the highest possible rating—from Charity Navigator.

Environmental toxins implicated in rising rates of ASD, ADHD

Environmental toxins may play a key role in the rising rates of autism spectrum disorder (ASD) and attention-deficit/hyperactivity disorder (ADHD), according to a new study from researchers in the United States.

Surveying nearly 8,000 adults using a questionnaire designed to identify individuals with chemical intolerances, Raymond Palmer and colleagues found that parents with chemical intolerance scores in the top tenth percentile were 5.7 times more likely to report having a child with ASD compared to parents in the bottom tenth percentile. They also were 2.1 times more likely to report having a child with ADHD.

Senior study author Claudia Miller says, “This is the first-ever article in the medical literature showing that chemical intolerance in parents can predict the risk of autism and ADHD in their children, and suggests that reducing exposures prior to and during pregnancy could help prevention.”

In earlier research, Miller and colleagues detected a strong association between chemical intolerance and immune system cells called mast cells. When exposed to foreign substances such as chemicals, these cells can release inflammatory molecules. Once mast cells are sensitized, the researchers say, even low levels of exposure to the original toxin or other chemicals can lead to inflam-

mation. Their work suggests that increasing rates of autism and ADHD may be linked to toxic chemicals “turning on” or “turning off” critical mast cell genes, with these epigenetic changes being transmitted from one generation to the next.

The researchers caution that their current study cannot determine the cause of the association between chemical sensitivity and ASD or ADHD, and they stress that more research on this topic is needed. They conclude, “The potential role of environmental toxicants in influencing epigenetics and mast cell function is a complex and emerging area of research.... Acknowledging the need for further evidence, we hope this study contributes to an improved understanding of the potential role of environmental factors in the global rise of autism and ADHD.”

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“Assessing chemical intolerance in parents predicts the risk of autism and ADHD in their children,” Raymond F. Palmer, David Kattari, Rodolfo Rincon, and Claudia S. Miller, *Journal of Xenobiotics*, March 2024 (free online). Address: Raymond Palmer, Department of Family and Community Medicine, University of Texas Health Science Center at San Antonio, San Antonio, TX 78229, palmerr@uthscsa.edu.

—and—
“Parental avoidance of toxic exposures could help prevent autism, ADHD in children, new study shows,” news release, University of Texas Health Science Center at San Antonio, March 28, 2024.

EDITORIAL: Stephen M. Edelson, Ph.D.

Fecal Microbiota Transplantation and Autism

Over the past several years, Fecal Microbiota Transplantation (FMT) has become the subject of growing interest in the autism community due, at least in part, to the increased awareness of the gut-brain relationship. Along with its possible significance, however, there are concerns regarding its safety and the need for evidence-based research to establish its effectiveness. This editorial discusses the various aspects of FMT, describes potential benefits, and outlines critical issues that must be addressed.

Gastrointestinal Disease in Autism

In 2010, a consensus report on gastrointestinal (GI) disorders in individuals with autism spectrum disorder (ASD) was published in *Pediatrics*, sparking widespread research focused on causes and treatment (1). GI problems found to be common in individuals on the autism spectrum include chronic constipation, diarrhea, abdominal pain, and gastroesophageal reflux disease (GERD) (2). The causes of these disorders are multifaceted, and numerous studies have documented some commonalities including reduced bacterial diversity and dysbiosis (3,4). Moreover, many of these GI disturbances have been found to be associated with co-occurring conditions such as anxiety, sleep disturbances, and various behavioral disorders, such as aggressive, repetitive, and self-injurious behaviors. (5).

Fecal Microbiota Transplantation

FMT involves the transferring of fecal microbes from a healthy donor into the GI tract of a patient. This procedure is often beneficial in treating recurrent *Clostridioides difficile* infections (CDI) (6) and is being investigated in clinical trials for other gut conditions, including ulcerative colitis (7).

The lack of standardization in the preparation and delivery of fecal microbes and in donor selection poses significant challenges (8,9). The microbes are obtained from donor fecal material. The preparation process involves meticulous screening of donors for past and current GI issues, chronic illnesses, and infectious diseases such as HIV and hepatitis. In addition, the donor's fecal microbes may be tested to ensure a diverse and healthy gut microbiota. The fecal material is administered to a suitable patient via oral capsules, liquid solutions, nasogastric tube, enema, or direct placement in the colon or upper GI tract via endoscopy (10). The American Gastroenterological Association is currently developing guidelines for the use of FMT (11).

It is important to understand that CDI is fundamentally different from most other disorders that may be associated with an altered gut microbiota. CDI is a complication of antibiotic therapies, and the disorder is also treated with antibiotics. Many patients develop recurrent CDI because antibiotics cannot eliminate *C. difficile* spores from their intestines. Repeated antibiotic treatments result in an altered gut microbiome, which can then be restored with FMT. A single administration of donor microbiota is typically sufficient. This is not the case in most other conditions, where a single FMT dose will not achieve a significant and lasting change in the gut microbial composition. Modification of the gut microbiome in non-CDI conditions typically requires antibiotic conditioning and repeated dosing of donor microbiota. The precise protocols are still being investigated.

Safety Concerns and FDA Regulations

In 2019, the FDA issued a safety warning about the potential risk of serious adverse effects using FMT due to the transmission of harmful organisms (12). Two individuals had contracted *extended-spectrum beta-lactamase (ESBL)-producing Escherichia coli* (*E. coli*); one died, while the other recovered. They both received stool samples from the same donor. The *New England Journal of Medicine* later published a detailed description of each case (13). In 2020, the FDA issued another safety warning with regard to two individuals who contracted Shiga toxin-producing *Escherichia coli* (STEC) infection as the result of FMT and subsequently died (14). These patients had both received the STEC infection from the same donor. Both patients were at risk of bacterial infections because of weakened immune systems. Additionally, four other individuals were hospitalized due to an infection with enteropathogenic *Escherichia coli* (EPEC), which they acquired from two different donors. All six patients had undergone FMT from fecal matter provided by OpenBiome (15).

In a 2022 review and meta-analysis that examined data from 61 studies involving nearly 5,100 patients, researchers found that serious adverse effects of FMT were relatively rare, occurring in less than 1% of the cases (16). These serious effects included sepsis or sepsis-like conditions (0.19%), aspiration pneumonia (0.27%), and bowel perforation (0.20%). More common, although less severe, adverse effects included constipation (1.03%), abdominal pain (1.66%), nausea (0.92%), vomiting (0.34%), flatulence (0.70%), and febrile episodes (0.33%).

In that same year, and in response to these safety concerns, the FDA published guidelines and regulations to improve safety, including screening for STEC and EPEC infections. Subsequently, in November 2022, the FDA approved the first fecal microbiota product for rectal administration to treat CDI (17), followed by an oral version of a subset of bacteria specifically tailored for CDI (18). These approvals were specific to individuals aged 18 years and older and were not explicitly extended to autistic individuals. These products involve 1 to 2 doses, which is sufficient for treating CDI. However, daily dosages for 8 weeks have been used for treating GI problems in autism. Moreover, the FDA's approval of FMT was confined to the treatment of CDI and did not encompass other gut disorders.

A national registry has now been established to gather clinical and patient-reported outcomes with the primary goal of evaluating the safety of FMT over both short-term and long-term periods (19). This registry is sponsored by the American Gastroenterological Association (AGA) Institute in collaboration with the Crohn's and Colitis Foundation of America, the Infectious Diseases Society of America, and the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition.

The potential risk of bacterial infection can be drastically reduced with adequate donor selection and the testing of donor stool prior to administration to patients. Donor selection criteria are now very rigorous in their exclusion criteria and are needed to ensure that donors do not have any health conditions that may be associated with gut microbiota dysfunction. This means donors are metabolically fit, take no medications, and have no risk factors for autoimmunity, cancer, atopic disorders, or neuropsychiatric problems.

Research on FMT and Autism

Although research into the effectiveness of FMT in treating GI disease in autistic individuals is still in its early stages, several non-blinded studies involving autistic children have been carried out (20-24). Because these studies are open-label, which means both the researchers and participants know about the treatment being given, there is an increased possibility of bias.

In one study involving 18 autistic children with moderate to severe GI disease, as well as a control group of 20 neurotypical children without GI issues, autistic participants exhibited improvements in gut bacterial diversity (20,21) and a reduction in GI

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Research Updates

Physical activity may help to ease sleep problems in children with ASD

Physical activity may play a significant role in reducing sleep problems in children with autism spectrum disorders (ASD), according to a meta-analysis by researchers in China and the United States.

Sleep problems are one of the most common issues for children with ASD, affecting as many as 80% of this population. Poor sleep can contribute to fatigue, daytime behavior problems, and cognitive issues, as well as causing stress for families.

In their meta-analysis, Xiao Liang and colleagues reviewed eight studies on the effects of physical activity programs on sleep in individuals with ASD. “Compared to no-treatment control groups,” they say, “physical activity interventions had a large positive effect on parent-reported general sleep problems, night awakenings, sleep resistance, sleep duration, and actigraphy-assessed sleep efficiency in children and adolescents with ASD.”

The researchers suggest, “As an efficacious lifestyle intervention, physical activity intervention is low-cost and easy to implement as it is a joyful and child-appropriate approach.”

“The impact of the physical activity intervention on sleep in children and adolescents with autism spectrum disorder: A systematic review and meta-analysis,” Xiao Liang, Justin A. Haegele, Andy Choi-Yeung Tse, Minghui Li, Hui Zhang, Shi Zhao, and Shirley Xin Li, *Sleep Medicine Reviews*, April 2024 (online). Address: Xiao Liang, Department of Rehabilitation Sciences, The Hong Kong Polytechnic University, Hong Kong SAR, China, shawn.liang@polyu.edu.hk.

Sensory integration therapy found beneficial for kids with ASD, related issues

A meta-analysis by researchers in South Korea indicates that sensory integration therapy can be beneficial for many children with autism spectrum disorders (ASD). This type of therapy is designed to reduce sensory processing problems, a common challenge for children with ASD, by exposing them in a structured way to sensory input—particularly tactile, auditory, proprioceptive, and vestibular input.

Seri Oh and colleagues analyzed data from 24 Korean studies involving the use of sensory integration interventions. The researchers say their analysis indicates that the therapy can be effective for children with

ASD as well as those with related disabilities including cerebral palsy, attention/deficit hyperactivity disorder, developmental disorder, and intellectual disability. In addition to improving sensory processing, they say, sensory integration therapy appears to enhance social skills, adaptive behavior, and gross and fine motor skills.

“Regarding sensory integration therapies,” they add, “1:1 individual treatment with a therapist or a therapy session lasting for 40 min was most effective.”

The researchers conclude, “The results of this study may be used as therapeutic evidence for sensory integration intervention in the clinical field of occupational therapy for children, and can help to present standards for sensory integration intervention protocols.”

“Effectiveness of sensory integration therapy in children, focusing on Korean children: A systematic review and meta-analysis,” Seri Oh, Jong-Sik Jang, A-Ra Jeon, Geonwoo Kim, Mihwa Kwon, Bahoe Cho, and Narae Lee, *World Journal of Clinical Cases*, March 6, 2024 (online). Address: Narae Lee, Department of Occupational Therapy, U1 University, Chung-cheong bukdo 25949, South Korea. nereis1004@gmail.com.

DEALING WITH SLEEP PROBLEMS OR SELF-INJURIOUS BEHAVIORS?

ARI’s free online tools can assist professionals and parents in identifying treatments that may reduce or eliminate self-injurious behavior or sleep disturbances in clients or family members with autism spectrum disorders (ASD).

Understanding and Treating Sleep Disturbances Survey Tool

www.SleepDisturbances.com

Understanding and Treating Self-Injurious Behavior Survey Tool

www.Self-InjuriousBehavior.com

Are you an adult with autism?

Increasing numbers of adults are being diagnosed with autism spectrum disorders (ASD). To learn more about the symptoms of autism in adults, see ARI’s article at:

<https://autism.org/autism-symptoms-and-diagnosis-in-adults/>

Prenatal anesthesia may increase odds of ASD

Prenatal exposure to anesthesia may increase the likelihood of a child developing an autism spectrum disorder (ASD), according to a new study from Columbia University.

In the study, Caleb Ing and colleagues compared 34,271 children exposed prenatally to anesthesia to 171,355 unexposed children, matching each exposed child with five controls. The mothers of the exposed children had undergone either an appendectomy or a cholecystectomy during pregnancy. The researchers controlled for a variety of factors including age, race, ethnicity, state of residence, income, and Medicaid enrollment for disability or poverty.

The researchers found that prenatally exposed children were 31 percent more likely than controls to receive a diagnosis of a disruptive or internalizing behavioral disorder. (Disruptive behavioural disorders include attention-deficit/hyperactivity disorder as well as conduct, impulse control, or oppositional defiant disorders; internalising behavioural disorders include bipolar disorder, depression, and anxiety). The increased likelihood of children being diagnosed with ASD was also 31%.

Study coauthor Guohua Li comments, “Our findings could help inform preoperative risk assessment in pregnant women, especially when the surgical procedure is elective or when viable treatment is available. Results of this study also give added impetus to research on safer anesthetic drugs and techniques.”

“However,” Ing says, “caution is advised, as many procedures in pregnant women may be necessary, and avoidance of necessary procedures can have detrimental effects on mothers and their children.”

“Behavioural disorders after prenatal exposure to anaesthesia for maternal surgery,” Caleb Ing, Jeffrey H. Silber, Deven Lackraj, Mark Olfson, Caleb Miles, Joseph G. Reiter, Siddharth Jain, Stanford Chihuri, Ling Guo, Cynthia Gyamfi-Bannerman, Melanie Wall, and Guohua Li, *British Journal of Anaesthesia*, February 28, 2024 (online). Address: Caleb Ing, ci2119@cumc.columbia.edu.

—and—

“Uptick in behavioral disorders reported in children following prenatal exposure to anesthesia,” news release, Columbia University Mailman School of Public Health, February 29, 2024.

Moving?

Please let us know well in advance, so your next issue will reach you on time!

Research Updates

“Earlier is better” for school programs for kids with ASD

More data indicating that early intervention is important when it comes to educational programs for children with autism spectrum disorders (ASD) comes from a new study by researchers in Israel.

Ronit Saban-Bezalel and colleagues examined the outcomes of two groups of children with ASD after one year of attending special education classes. One group included 35 children between 34 and 59 months of age, and the other included 38 children between 60 and 91 months of age. At baseline, the two groups did not differ in cognitive ability, autism severity, or adaptive behavioral skills.

The researchers say that while both groups improved significantly, the benefits were much more pronounced for the younger children. When tested, they say, “only younger children showed a significant decrease in the severity of communication, awareness and restricted interests and repetitive behavior subdomains and a significant increase in motor adaptive skills. Younger children also showed more remarkable improvement in the naming and expressive subdomains.” They add, “Respectively, older age predicted more severe ASD symptoms at the end of the educational year.”

The researchers conclude, “Corresponding to brain plasticity theories, our findings point to an association between age and outcomes. The findings should serve as a benchmark for policymakers regarding early intervention in young children with autism.”

“Younger age is associated with better outcomes in autism severity, language, and adaptive skills after one school year in autism special education classes,” Ronit Saban-Bezalel, Ditza A. Zachor, Einat Avni, and Esther Ben-Itzhak, *Research in Autism Spectrum Disorders*, May 2024 (online). Address: Ronit Saban-Bezalel, Bruckner Center for Autism Research, Department of Communication Disorders, Ariel University, Ariel 40700, Israel, Ronitsa@ariel.ac.il.

Study hints that nonverbal people with ASD may have surprising grasp of written language conventions

Many nonverbal or minimally verbal individuals with autism spectrum disorders (ASD) appear to have some understanding of written language conventions, according to researchers at the University of Virginia.

Vikram Jaswal and colleagues enrolled 31 nonverbal or minimally verbal autistic teenagers and adults in their study. Participants played an iPad game that involved tapping flashing letters, and the researchers examined the speed at which they tapped the letters.

Analyzing the results, the researchers found that about half of the participants exhibited patterns indicating that they knew how to spell:

- They tapped flashing letters faster when the letters spelled out sentences than when the letters made no sense.
- They tapped letters that usually go together faster than letters that do not usually go together.
- They paused before tapping the first letter of a new word, indicating that they knew where one word ended and the next word began.

The researchers say, “These findings suggest that nonspeaking autistic people can acquire foundational literacy skills. With appropriate instruction and support, it might be possible to harness these skills to provide nonspeaking autistic people access to written forms of communication as an alternative to speech.”

However, the researchers caution that their sample was small and that participants had all had at least one year of experience learning to spell words and sentences on a letterboard. They say, “We do not know

whether nonspeaking autistic people who did not have that experience would perform similarly.” Additionally, they say, “It is possible that the literacy skills documented here could be acquired without any connection to meaning, as in some accounts of hyperlexia.”

“Literacy in nonspeaking autistic people,” Vikram K Jaswal, Andrew J Lampi, and Kayden M Stockwell, *Autism*, March 2024 (free online). Address: Vikram K Jaswal, Department of Psychology, University of Virginia, PO Box 400400, Charlottesville, VA 22904-4400, jaswal@virginia.edu.

—and—
“Study reveals unexpected literacy in autistic people who cannot speak,” news release, University of Virginia College and Graduate School of Arts & Sciences, March 6, 2024.

Research suggests link between air pollution, ASD

A study by researchers in China and Australia adds to evidence implicating air pollution as a factor in autism spectrum disorders (ASD).

Tianyu Jin and colleagues used an approach called Mendelian randomization to study the relationship between air pollution and ASD. Mendelian randomization is a technique that helps to overcome some of the limitations of observational studies.

The researchers focused on two types of particulates: PM₁₀, which has a diameter of 10 microns or less, and PM_{2.5}, which has a diameter of 2.5 microns or less. They report that while no causal association was seen between PM₁₀ and ASD, “Our results indicated that PM_{2.5} and PM_{2.5} absorbance might increase the risk of ASD.”

They conclude, “As urbanization and industrial activities continue to burgeon, it becomes imperative to address air pollution as a modifiable risk factor.”

“Particulate matter 2.5 causally increased genetic risk of autism spectrum disorder,” Tianyu Jin, Qiongyi Pang, Wei Huang, Dalin Xing, Zitian He, Zheng Cao, and Tong Zhang, *BMC Psychiatry*, February 2024 (free online). Address: Tong Zhang, Department of Rehabilitation Medicine, The Second Affiliated Hospital and Yuying Children’s Hospital of Wenzhou Medical University, Wenzhou, Zhejiang, China, tomzhang@126.com

Visit the National Autism History Museum

To mark nearly a century of written history of autism, the Autism Research Institute (ARI) recently opened the National Autism History Museum—the first historical museum dedicated to autism. The four-room museum is located in the Kensington district in San Diego, California, adjacent to ARI’s main office. For more information about the museum and to watch an overview video, visit www.autism.org/visiting-aris-national-autism-history-museum.

Hours:

Monday-Thursday 10 a.m. to noon. or by appointment. To make an appointment, email us at NationalAutismHistoryMuseum@autism.org or call 833-281-7165.

Need help or information?

The Autism Research Institute maintains a toll-free calling center:

833-281-7165

Large-scale study detects early alterations in the gut flora of children who later develop ASD

A large-scale study by researchers in Sweden, Finland, and the United States indicates that alterations in gut flora during infancy are associated with an increased likelihood of a child developing autism spectrum disorder (ASD) or another neurodevelopmental disorder (ND).

Angelica Ahrens and colleagues analyzed data collected on more than 16,000 children followed through the All Babies in Southeast Sweden (ABIS) study. Of the children, nearly 1,200 had been diagnosed with ASD, attention-deficit/hyperactivity disorder

Senior study author Johnny Ludvigsson says, “We can see in the study that there are clear differences in the intestinal flora already during the first year of life between those who develop autism or ADHD and those who don’t.”

der (ADHD), a communication disorder, or intellectual disability. Using extensive information collected on the ABIS cohort, the researchers looked for biological and environmental factors associated with an ND diagnosis. In addition, for a subset of children, they analyzed umbilical cord blood samples taken at birth and stool samples collected at one year of age.

Senior study author Johnny Ludvigsson says, “We can see in the study that there are clear differences in the intestinal flora already during the first year of life between those who develop autism or ADHD and those who don’t.” For example, a number of bacteria that contribute to optimal gut health, including *Akkermansia*, *Bifidobacterium*, *Ruminococcus*, and *Faecalibacterium*, were deficient in infants later diagnosed with NDs.

The researchers also found that children who experienced repeated ear infections early in life had increased odds of being diagnosed with an ND. They speculate that this was due not to the infections themselves, but to treatment with antibiotics. Their analysis showed that penicillin use when children were between one and two-and-a-half years of age resulted in a 1.6-fold higher likelihood of future ASD, and that children with future ASD were also more

likely to have received non-penicillin antibiotics during this period.

Ahrens comments, “We’re not trying to say that antibiotics are necessarily a bad thing. But perhaps overuse can be detrimental to the microbiome, and for some children, for whatever reason, their microbiome might not recover as readily.”

Early gastrointestinal problems and mood disorders were also more common in children who later developed NDs. In addition, children born preterm were more likely to be diagnosed with NDs.

The researchers also compared substances in the umbilical cord blood of 27 children diagnosed with ASD with samples from controls. They found that children later diagnosed with ASD had low umbilical cord blood levels of linolenic acid, an essential fatty acid. In addition, they had higher levels than controls of chemicals in the PFAS category. These substances, used as flame retardants, are harmful to the immune system.

The researchers found that a number of additional factors—for instance, stress, exposure to tobacco smoke, and an HLA genotype associated with inflammation—increased the likelihood of a child develop-

ing an ND. However, they note that even when they accounted for these factors, the link between gut flora alterations and a future diagnosis of ND remained significant for many of the bacteria.

“Collectively,” the researchers say, “our findings suggest that an inflammatory stage, mediated by gut bacteria, may contribute to ND risk very early in life.” They add, “Our study emphasizes the need for further research on dysbiosis persistence and functional consequences across early childhood, crucial for developing optimal interventions and understanding causality.”

“Infant microbes and metabolites point to childhood neurodevelopmental disorders,” Angelica P. Ahrens, Tuulia Hyötyläinen, Joseph R. Petrone, Kajsa Igelström, Christian D. George, Timothy J. Garrett, Matej Orešič, Eric W. Triplett, and Johnny Ludvigsson, *Cell*, April 3, 2024 (free online). Address: Eric Triplett, ewt@ufl.edu.

“UF and Swedish researchers connect childhood microbiome with development of autism, ADHD,” Megan Winslow, University of Florida UF/IFAS Blogs, April 3, 2024.

“Autism and ADHD are linked to disturbed gut flora very early in life,” news release, Linköping University April 4, 2024.

Playing “serious” games may benefit children, teens with ASD

A new meta-analysis by researchers in Portugal suggests that playing “serious” games—that is, games that focus on teaching knowledge or skills, rather than on providing entertainment—can have benefits for children and teens with autism spectrum disorders (ASD).

Tânia Carneiro and colleagues identified nine studies on the use of serious games by individuals with ASD that met criteria for inclusion in their analysis. Reviewing the studies, the researchers found “a positive influence of serious games on social skills and related domains, encompassing emotion recognition/encoding/decoding, emotional regulation, eye gaze, joint attention, and behavioral skills.”

They add, “One notable aspect of our findings is the role of serious games in addressing the specific challenges faced by individuals with ASD. Engaging with these

children in face-to-face settings can often be difficult due to the lack of learner interest. Therefore, the characteristics of serious games, such as the use of visual cues, the incorporation of dynamic and appealing characters, the opportunity to choose among various activities and environments, the opportunity for autonomy within the gaming environment, and the possibility for caregivers to be present, benefit these children and cater to this population’s unique needs and preferences.”

The researchers caution that their findings are limited by factors including the potential for bias, the relatively small number of participants in the studies, and the wide range of interventions studied. In addition, they say, “While participative and collaborative games show promise for this population, concerns could also arise regarding the potential for increased isolation and other associated risks.” However, they say, “The promising outcomes suggest that serious games serve as effective interventions to enhance social skills.”

“Serious games for developing social skills in children and adolescents with autism spectrum disorder: a systematic review,” Tânia Carneiro, António Carvalho, Sónia Frota, and Marisa G. Filipe, *Healthcare*, February 20, 2024 (free online). Address: Marisa Filipe, Center of Linguistics, School of Arts and Humanities, University of Lisbon, 1600-214 Lisboa, Portugal marisa.filipe@campus.ul.pt.

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Editorial: Fecal Microbiota Transplantation and Autism (continued from page 3)

symptoms, as well as improvements in social interaction and adaptive behaviors (20). In this study, adverse effects of FMT were limited. One child developed a long-term rash during vancomycin treatment prior to receiving FMT. Additionally, 12 children experienced mild hyperactivity or tantrums for 1 to 3 days. FMT was generally well-tolerated in both rectal and oral forms, with the exception of one child who vomited during high-dose oral administration and was subsequently switched to the rectal route. Overall, the study observed only temporary and minor adverse effects. A follow-up study two years later suggested continued benefits from the initial FMT trial (22).

More recently, a separate independent research team conducted a study, utilizing similar assessment measures, that largely replicated the findings described above (23). This included a larger sample size of 40 autistic children, all experiencing GI issues, and a comparison group consisting of 16 age- and sex-matched neurotypical children

without GI problems. Short-term adverse effects were noted, including fever (3.7%), hyperactivity (11.4%), and tantrums/aggression (3.7%). This study observed that the benefits from FMT began to diminish within a few weeks after the therapy ended, leading the authors to suggest the potential need for additional treatment.

Another study explored the possible long-term benefits of FMT over a five-year period (24). This retrospective study examined 328 autistic children without a control group and utilized assessment tools similar to those used in the earlier studies. The findings indicated that improvements were sustained for approximately four years, but returned to baseline by the five-year follow-up. These data suggest the lack of prolonged benefit.

Concluding Remarks

While open-label studies suggest the potential for FMT to benefit autistic individuals with GI disorders, double-blind, multi-site trials are critical to definitively assess efficacy and safety. Some of these trials are already underway (25). Additionally, immune (26,27) impairments, oc-

asionally observed in autistic individuals, may require special attention when providing FMT. Should FMT ever be approved for the treatment of autism, meticulous adherence to FDA-approved preparation and administration procedures by physicians will be critical to ensure patient safety and treatment efficacy.

Moreover, there are only a limited number of studies, both with and without autistic participants, to assess whether periodic doses throughout an individual's lifetime are necessary. This necessity may depend on various factors, such as age, GI condition, and the route of administration, among others.

In summary, FMT holds promise as an effective intervention for some autistic individuals, but the treatment remains experimental and without proven efficacy. Dosage, standardization, and safety have yet to be established. As more is learned, it is essential to weigh the potential efficacy of a new treatment for autistic individuals with these GI issues against concerns about safety.

References are available at
www.ARRIReferences.org.

IN MEMORIAM

Anne M. Donnellan, a pioneer in the autism field, passed away on March 22, 2024. A researcher, advocate, and educator, Dr. Donnellan founded Los Niños—one of the first programs in the world for autistic children—in San Diego, California. Her groundbreaking work emphasized studying movement differences in autism, and she authored a number of influential books including *Autism: Sensory-Movement Differences and Diversity* (with Martha R. Leary), *Alternatives to Punishment* (with Gary LaVigna), and *Progress without Punishment* (with Gary LaVigna, Nanette Negri-Shoultz, and Lynette Fassbender). She was a professor in the School of Leadership and Education Sciences at the University of San Diego and Director of the USD Autism Institute.

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Maternal vitamin D, multivitamin use may lower odds of ASD

Children of mothers who take multivitamins and/or vitamin D during pregnancy may have reduced odds of receiving a diagnosis of autism spectrum disorder (ASD), according to a large-scale study from China.

Xiujie Qi and colleagues analyzed data collected on 1,321 children with ASD and 1,200 neurotypical children enrolled in the China Multi-Center Preschool Autism Project from May 2018 to December 2019. The researchers divided the mothers into three categories: those who took vitamin D supplements, those who took multivitamins (with or without vitamin D), and those who did not take either one.

The researchers investigated both the incidence of ASD in the women's children and the severity of symptoms in children who did develop ASD. Symptoms were assessed using the Autism Behavior Checklist (ABC), the Social Responsiveness Scale (SRS), and the Childhood Autism Rating Scale (CARS), while neurodevelopmental levels were assessed using the Children Neuropsychological and Behavior Scale-Revision 2016 (CNBS-R2016).

The researchers report that maternal vitamin D and multivitamin supplementation during pregnancy were both significantly associated with a lower likelihood of ASD in children. Children with ASD whose mothers took multivitamins during pregnancy had lower CARS scores, fewer com-

munication problems, and higher personal-social scores than children of mothers who did not take supplements. Maternal vitamin D supplementation did not influence symptoms or developmental scores in children with ASD.

The researchers conclude, "This study supports a protective association between maternal vitamin D and multivitamin supplementation during pregnancy and the risk of ASD in offspring." In addition, they say, "Maternal multivitamin supplementation may potentially moderate the symptoms and personal-social ability in ASD children."

"Maternal multivitamin supplementation is associated with symptoms in offspring with autism spectrum disorder: A multi-center study in China," Xiujie Qi, Ting Yang, Jie Chen, Li Chen, Ying Dai, Hua Wei, Feiyong Jia, Lijie Wu, Yan Hao, Ling Li, Jie Zhang, Xiaoyan Ke, Mingji Yi, Qi Hong, Jinjin Chen, Shuanfeng Fang, Yichao Wang, Qi Wang, Chunhua Jin, and Tingyu Li, *Research in Autism Spectrum Disorders*, March 2024 (online). Address: Tingyu Li, Children's Hospital of Chongqing Medical University, Chongqing Key Laboratory of Childhood Nutrition and Health, National Clinical Research Center for Child Health and Disorders, Ministry of Education Key Laboratory of Child Development and Disorders, Chongqing 400014, China, tyli@vip.sina.com.

—and—

"Maternal vitamin D, multivitamin supplementation may reduce risk of autism in offspring," Erin Hunter, *Pharmacy Times*, February 2, 2024.

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